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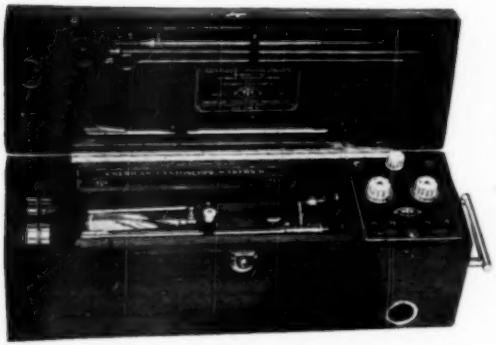

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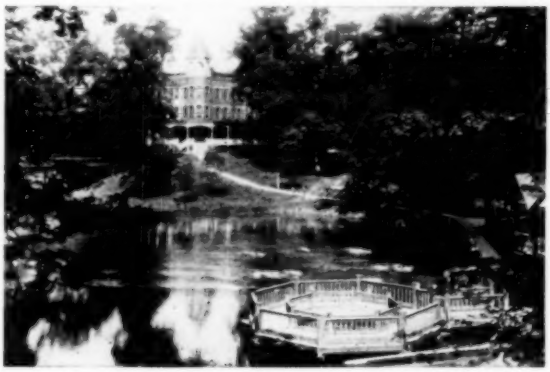

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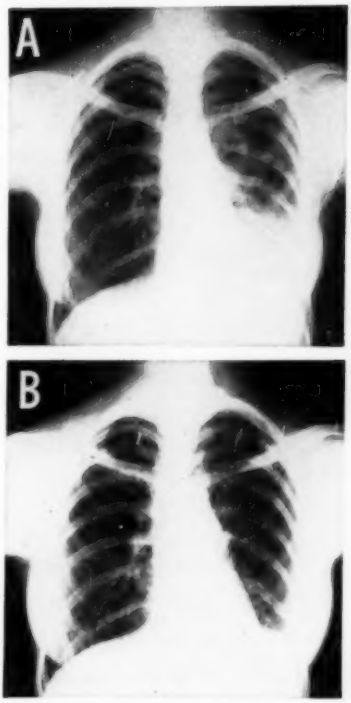

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SARCOIDOSIS

A Clinical and Roentgenological Study of Twenty-eight Cases

JOHN H. MOYER[1] AND ALFRED J. ACKERMAN

(Received for publication August 26, 1949)

INTRODUCTION

Sarcoid lesions involving various organs are no longer regarded as separate disease entities, but rather as pleomorphic manifestations of a generalized chronic disease which may involve many organs simultaneously and successively. Acute generalized phases of the pathological process alternate with varying degrees of remission and specific organ localization such as the skin (4), or the skeletal system (12), et cetera. Study of the group of patients in the present report lends additional support to the concept of the disseminated character of the disease by the findings of: electrocardiographic abnormalities, disseminated pulmonary lesions on roentgenographic studies, biochemical and histological evidence of liver involvement in a high percentage of those patients thus examined, and bony changes similar to those seen in rheumatoid arthritis. The sarcoid lesions apparently spare no particular organ.

The definitive diagnosis depends upon the discovery of typical histological lesions of sarcoidosis. This is usually an easy matter during an acute exacerbation with dissemination of the disease. In the more chronic latent form even repeated biopsies of nodes or other accessible tissues may prove inconclusive.

This presentation is based upon 28 cases of sarcoidosis, proved histologically, 19 of which were studied in an army center. Eleven patients of the group were entirely asymptomatic and were admitted only because of abnormalities in chest roentgenograms. The majority of the patients were observed for periods of six months to two years; a few were followed for as long as five years.

CLINICAL MANIFESTATIONS

General Considerations

Sarcoidosis may occur at any age, but the incidence is particularly high between 15 and 35 years of age (21, 26). The average age of the patients in the present study was 23 years. The racial distribution differs somewhat in individual

[1] Department of Medicine, Baylor University School of Medicine, Houston, Texas; formerly University of Pennsylvania, School of Medicine, Philadelphia, Pa.

reports, but the higher frequency of sarcoid lesions in Negroes as compared to whites is a common experience of all observers in this country.

The clinical features of sarcoidosis are those of a low-grade, chronic granuloma. Although repeated exacerbations and remissions are the rule, complete regression of disease has been noted in about 25 per cent of patients. In an equal percentage, the lesions assume a chronic character in which no significant fluctuations of activity occur (26).

Constitutional symptoms may be transient or entirely absent. They are rarely severe, but may occasionally persist for years. These symptoms are more common in the acute, generalized state. They include various degrees of fatigue, malaise, weakness, weight loss, joint pain, low-grade fever, anorexia, and dyspnea. During the chronic phase of the disease there may be no symptoms despite histologic evidence of permanent visceral damage. Progression of disease may occur at any time, even years after it has apparently become completely stabilized. One patient was observed who was entirely asymptomatic with persisting roentgenologic evidence of mediastinal adenopathy for at least five years. During this time, examination of material from repeated peripheral lymph node biopsies and biopsy of the tonsil was negative for sarcoidosis. Five years after first coming under observation, the patient suddenly developed a generalized peripheral lymphadenopathy and mild constitutional complaints. A biopsy of an axillary node at this time yielded material which showed numerous lesions of sarcoid.

The prognosis both as to morbidity and mortality depends on the organ involved and the degree of permanent functional impairment. Thus permanent blindness may result from severe iridocyclitis. Although rare, chronic disability and eventual death may result from cardiac and or respiratory insufficiency.

Intrathoracic Manifestations

Sarcoidosis affects the tracheobronchial and mediastinal lymph nodes, the pulmonary parenchyma, and in some instances the cardiovascular system.

Tracheobronchial and mediastinal lymph node involvement: Intrathoracic adenopathy is rarely the only manifestation of sarcoidosis and is usually associated with concomitant involvement of the pulmonary parenchyma. The nodes are nearly always enlarged bilaterally and symmetrically. Occasionally cases with unilateral enlargement of the intrathoracic nodes are observed (Case 2). The enlargement may range from "prominent hilar shadows" to large tumefactions extending far into the lung fields, similar to lymphosarcoma or Hodgkin's sarcoma. The lung roots are usually prominent. In the writers' experience enlarged nodes do not appreciably affect adjacent structures. Symptoms due to pressure on large vessels or the esophagus are rarely present even in cases with extreme mediastinal adenopathy. In only one instance in the present series was it possible to demonstrate a traction diverticulum of the esophagus (1). The enlarged nodes frequently regress spontaneously over several months so that roentgenologic evidence of adenopathy may be lacking. This is of considerable value in distinguishing sarcoidosis from the lymphoblastomatous group of diseases in

which spontaneous remissions rarely occur. The absence of clinical symptoms in the presence of large mediastinal nodes is also of importance as an aid in the differential diagnosis. Only by histologic tissue studies, however, can the clinical or roentgenologic diagnosis of sardoidosis be conclusively proved.

CASE REPORTS

Case 1: A 26-year-old Negro male was admitted because of redness and pain of five days' duration in the right eye. He related a history of similar "inflammation" of his eyes recurring every six to eight months, and lasting several weeks for the past fifteen years. The patient had no other complaints. Examination of the eyes revealed bilateral iridocyclitis and chronic retinitis. Numerous heavy lardaceous deposits were noted on the posterior surfaces of the cornea. Small nodules were present on the pupillary border. On ophthalmoscopic examination, the retinal veins appeared markedly engorged and the disc was hyperemic. There were numerous flame-shaped hemorrhages in both retinae. Except for moderate inguinal adenopathy, the physical examination was otherwise noncontributory.

Laboratory studies: Routine examinations of blood and urine and a serologic test for syphilis were negative or normal. The erythrocyte sedimentation rate was 18 mm. per hour. A coccidioidin skin test was negative. The tuberculin test was negative using 0.001 and 0.5 mg. of PPD.

The serum proteins were 7.5 Gm. per 100 cc. with an A/G ratio of 4.2:3.3. The serum calcium and phosphorus were normal. An inguinal lymph node biopsy revealed sarcoidosis. Roentgenologic examination of the chest revealed bilateral enlargement of the paratracheal and parabronchial lymph nodes. The lung fields were clear.

Hospital course: The patient's only complaints were referable to his eyes. He was given a course of intravenous typhoid therapy by the eye department, following which he improved considerably. Examination after two months revealed only a subsiding iritis, with a few residual retinal hemorrhages. After six months, the patient was free of symptoms. There were a few residual retinal infiltrations due to the previous hemorrhages. The cornea was slightly vascularized. Roentgenograms of the chest revealed complete subsidence of the mediastinal and parabronchial adenopathy. The patient was subsequently discharged.

Case 2: A 31-year-old male was admitted because of chest pain, cough, and enlargement of the supraclavicular nodes. The physical examination was noncontributory. The total leukocyte count was 8,000 cells per cu. mm. with 3 per cent eosinophils. A bromsulfalein test showed 10 per cent retention after forty-five minutes.

Roentgenographic examination of the chest revealed a large, sharply defined mass in the left hilum, with a slightly scalloped, polycyclic border suggesting an enlarged node. The lung fields were clear. Examination of biopsy specimens from peripheral lymph nodes was negative. Serial roentgenographic examinations of the chest showed a marked regression of the mediastinal nodes. A fairly coarse, reticular fibrous infiltration in the left parahilar area developed which also regressed considerably within a few weeks. Two months after admission biopsy material from another peripheral node and from one tonsil showed typical lesions of sarcoid.

Pulmonary parenchymal involvement: There seems to be no correlation between the clinical symptoms and the extent of pulmonary parenchymal involvement which is demonstrated roentgenologically. A mild nonproductive cough is a frequent symptom. Although dyspnea, particularly on exertion, has been frequently recorded, this symptom was prominent in only approximately 30 per cent of the cases in the present series. Progressive dyspnea accompanies only

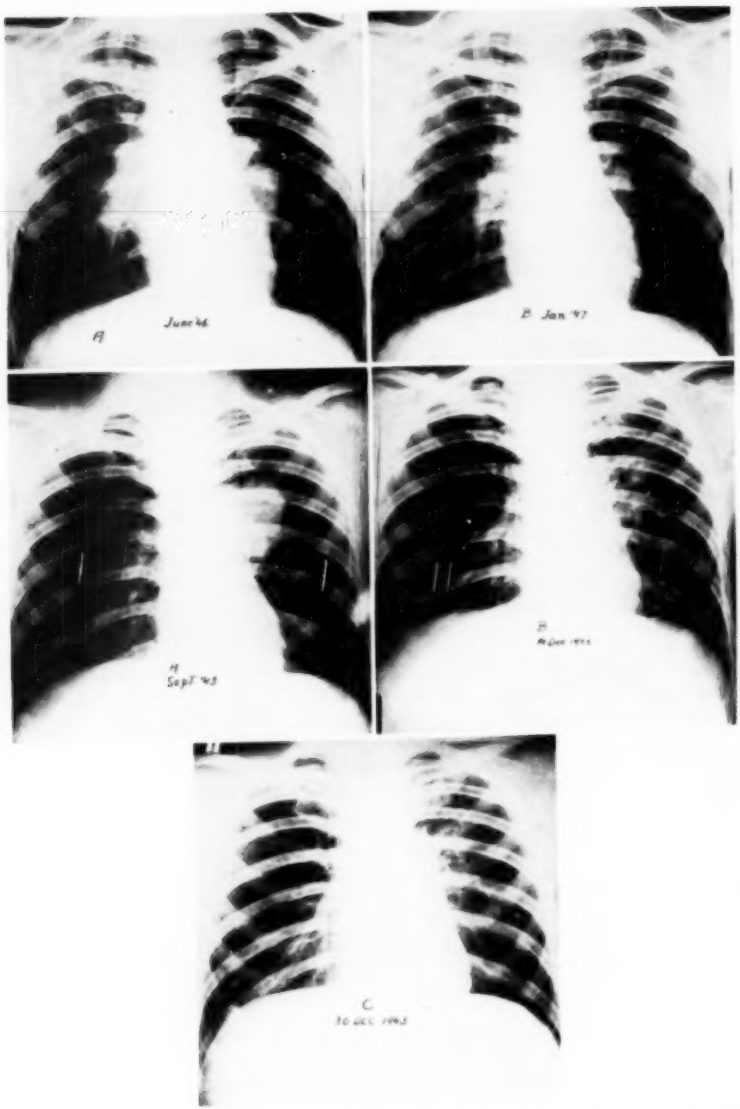

FIG. 1. Case 1. A. (Upper Left) The tracheobronchial and mediastinal nodes are enlarged.
B. (Upper right) The nodes have decreased in size; the lung fields are clear.
FIG. 2. Case 2. A. (Center left) Unilateral mediastinal adenopathy.
B. (Center right) The node has decreased in size; there is a parahilar infiltration on the left.
C. (Bottom) The pulmonary infiltration is also partly resolved.

progressive, extensive pulmonary involvement and/or cardiac failure (21). Significant findings are rarely elicited on physical examination.

The roentgenologic findings are variable. There are great individual differences in the distribution, extent, and character of the lesions. This is most likely a result of the fact that the roentgenologic findings represent different stages of evolution of the disease. Thus the outstanding roentgenologic feature observed in the early stage may become superseded by other changes during the subsequent phases of regression and progression.

Reisner (26) called attention to three main types of parenchymal lesions encountered in pulmonary sarcoidosis: diffusely disseminated small nodular infiltrations, diffuse or localized peribronchial fibrous infiltrations, and coalescent patchy infiltrations.

The diffusely disseminated infiltrations consist of discrete, small, nodular foci resembling in appearance and distribution those observed either in acute miliary or in chronic forms of hematogenous tuberculosis. At times the individual nodules, which occur in the interstitial lymphoid tissue of the lung parenchyma, attain a large size possibly due to coalescence of smaller foci. The lesions may be distributed uniformly throughout both lungs, or they may be confined to the parahilar or basal segments of the lungs.

The diffuse or localized infiltrations of a linear or strand-like character generally follow the distribution of the bronchovascular pattern, and are characterized roentgenologically by prominent root trunks and peripheral markings. A combination of the disseminated nodular form and the linear "peribronchial-perivascular" pattern occurs quite often.

Coalescent, patchy densities are usually observed along with widespread peribronchial-perivascular and nodular infiltrations. Lesions of this type can be widely distributed, but they are usually more frequent in the mid-zones and basal segments.

The various types of pulmonary lesions encountered in sarcoidosis are only an expression of different stages of evolution. Transitions from one type of infiltration into another and any combination of the fundamental patterns are frequently present together. A complete absorption of some areas of infiltration is seen almost invariably in cases remaining under prolonged clinical observation. The developmental cycle of pulmonary sarcoidosis is difficult to determine. The writers are in agreement with Reisner's concept (26) that the disseminated nodular forms are most likely to be associated with an early stage of the disease. The more bizarre forms, such as the linear interstitial fibrotic type and the conglomerate densities, can best be regarded as expressions of an intermediate or late phase. These latter forms are probably irreversible.

Occasionally sarcoid lesions are found in the lung parenchyma without concomitant enlargement of the mediastinal or tracheobronchial nodes. It cannot be stated definitely, however, that the nodes, even though not enlarged, are free from disease or that these nodes had not been enlarged during an earlier stage of the disease. Certainly, histologic evidence of sarcoidosis can be found in peripheral nodes in the absence of detectable adenopathy on physical examination. By the same token, a sudden progression of adenopathy may take place in the presence of an apparently subsiding process.

Parenchymal cavities have been reported in cases of pulmonary sarcoidosis by one group of observers (14). The accuracy of this observation is doubtful, however, in the absence of coexisting tuberculosis. This opinion is based on the facts that tuberculosis and sarcoidosis are frequently present simultaneously in the same individual (23, 26), and in many instances roentgenologically suggestive "typical" cavities in the midst of parenchymal lesions are the effect of summation of shadows simulating cavities. Laminographic studies for more accurate interpretation are of great value in such a situation.

The following cases are representative of the various forms of parenchymal disease produced by sarcoidosis.

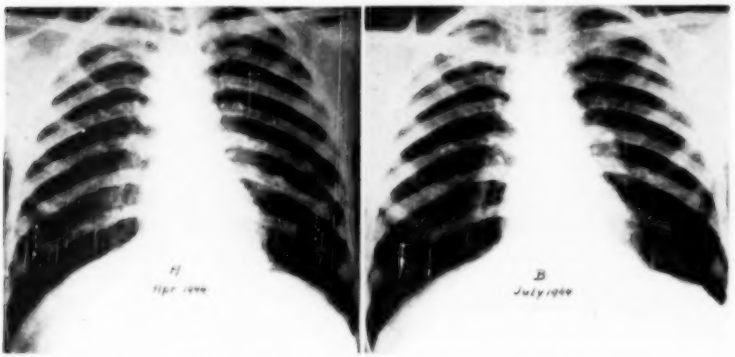

FIG. 3. Case 3. A. Diffuse miliary infiltration throughout both lung fields associated with moderate mediastinal adenopathy.

B. Complete resolution with restoration of normal lung fields.

CASE REPORTS

Case 2: A 23-year-old male was admitted because of shortness of breath, weakness, joint pains, and low-grade fever. Physical examination revealed rales at the base of the right lung and generalized lymphadenopathy. The temperature was 100°F. Laboratory studies were as follows: The total leukocyte count was 9,000 cells per cu. mm. with 10 per cent eosinophils. The erythrocyte sedimentation rate was 30 mm. per hour. The serum protein was 7.2 Gm. per 100 cc. with 3.2 Gm. of albumin and 4.0 Gm. of globulin. Twenty per cent retention of bromsulfalein was present after forty-five minutes. The cephalin flocculation test was 3 plus after forty-eight hours. The skin reaction to tuberculin was 1 plus, using 0.01 mg. PPD. Serum phosphorus and calcium were normal. Examination of material from a cervical lymph node biopsy revealed sarcoidosis.

Hospital course: The patient's symptoms did not change for about two months; he had low grade fever, weakness, and increasing dyspnea. Roentgenographic examination of the chest revealed a diffuse miliary infiltration throughout both lung fields. The mediastinal nodes were moderately enlarged. After alternating periods of regression and exacerbation, the patient improved gradually, and the pulmonary lesions resolved slowly. At the time of his dismissal from the hospital one year later, the lung fields were clear.

Case 4: A 20-year-old Negro male was admitted with numerous "nodular swellings" over the entire body and a generalized lymphadenopathy. The family and past history were

noncontributory. The patient was in no distress; there was no fever, pain, or cough. The skin lesions, which appeared approximately seven months prior to admission to the hospital showed no significant change in size, consistency, or color since the time they were first observed.

Physical examination revealed an enlargement of the lacrimal glands; hypertrophy of the conjunctivae; ptosis of the eyelids; enlarged cervical nodes; and widely disseminated, large nodular, subcutaneous lesions. These nodules measured 5 to 7 cm. in diameter and were most numerous on the trunk. The visceral organs showed no abnormality.

Laboratory findings: The total leukocyte and erythrocyte counts, the concentration of hemoglobin, and the differential leukocyte count were all within normal limits. Serum proteins, calcium, and phosphorus were normal. The skin reaction to tuberculin was 2 plus, using 0.10 mg. PPD. Roentgenographic examination of the chest showed rather diffuse peribronchial, fibronodular infiltration throughout the right lung field and the inner zone

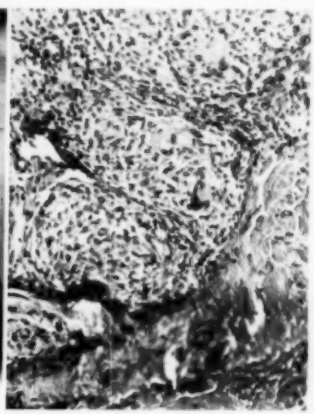

FIG. 4. Case 4. A. (Left) Diffuse fibronodular infiltration of the right lung and basal portion of the left; the mediastinal nodes are slightly enlarged.

FIG. 5. Case 4. (Right) Microscopic section of a cutaneous lesion × 170 B. G. H. Acc. No. 3413.

of the left lung field. The mediastinal nodes were slightly enlarged. Observation over seven months showed some regression of the pathologic process in the right lower lung field. Examination of biopsy material from a cutaneous lesion and a cervical node confirmed the clinical and radiologic diagnosis of sarcoidosis.

Case 5: A 19-year-old Negro male was admitted because of cough, shortness of breath, and low-grade fever. Physical examination was essentially negative. There was no peripheral adenopathy. The total erythrocyte and leukocyte counts were normal. The differential count showed 73 per cent neutrophils, 18 per cent lymphocytes, and 9 per cent eosinophils. The serum protein, calcium, and phosphorus were normal. The skin reaction to tuberculin was negative. The erythrocyte sedimentation rate was 15 mm. per hour. There was 25 per cent retention of bromsulfalein after forty-five minutes. Roentgenographic examination of the chest showed bilateral enlargement of the mediastinal nodes and a discrete miliary infiltration in both lower lung fields. During three months of observation, the mediastinal nodes regressed moderately, but the parenchymal infiltration extended farther and became more coarsely nodular in character. This exacerbation and extention of the process within

both lungs, demonstrated roentgenologically, was not accompanied by discernible clinical manifestations. The patient became free of symptoms soon after admission and remained so throughout the time of his hospitalization. It was possible, however, to prove the diagnosis of sarcoidosis histologically from a peripheral node and from material obtained by liver biopsy. On several occasions preceding the exacerbation, biopsies of peripheral nodes were noncontributory.

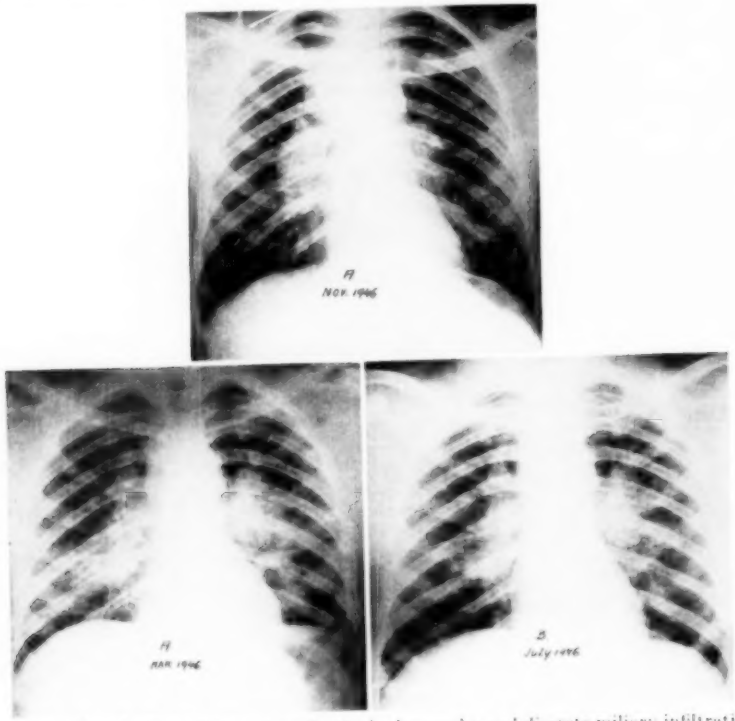

FIG. 6. Case 5. (Top) Bilateral mediastinal adenopathy and discrete miliary infiltration in both lower lung fields.

FIG. 7. Case 6. A. (Lower left) Mediastinal adenopathy and confluent parenchymal infiltration in both parahilar areas.

B. (Lower right) Diffuse fibronodular infiltration in both lung fields.

Case 6. A 25-year-old Negro male was admitted because of abnormal roentgenologic findings on a routine examination of the chest. He had no complaints. Physical examination revealed a temperature of 100 F., and a pulse rate of 90.

Laboratory studies showed normal urine and a negative serologic test for syphilis. The total leukocyte count was 8,000 cells per cu. mm. with 14 per cent eosinophils. Sputum studies were negative for tubercle bacilli. The erythrocyte sedimentation rate was 40 mm. per hour. The serum albumin was 4.0 Gm., and the serum globulin was 3.3 Gm. per 100 cc. The skin reaction to tuberculin was 2 plus. Serum calcium and phosphorus levels were normal. A bromsulfalein test revealed 20 per cent retention after forty-five minutes.

The cephalin flocculation was 2 plus after twenty-four hours, and 3 plus after forty-eight hours. The thymol turbidity test was positive, 9 units. Roentgenographic examination of the chest showed confluent parenchymal infiltrations in the parahilar areas and enlarged mediastinal nodes.

Hospital course: Examination of material from repeated biopsies of peripheral nodes was negative. Four months after admission, the patient had an acute recrudescent generalized lymphadenopathy and fever. Examination of tissue obtained from a *liver biopsy* at this time revealed sarcoidosis. Lymph node biopsy material also was positive for sarcoidosis. Repeated roentgenograms of the chest revealed increased density in the parahilar area due to more extensive nodular parenchymal infiltration. This did not change appreciably over a two-month period.

This case serves as another example of the variable states of activity exhibited by sarcoidosis. A chronic, asymptomatic phase was followed by acute exacerbation of symptoms, at which time accessible tissues (lymph node and liver) revealed generalized dissemination of the disease.

Case 7: A 25-year-old white male was admitted to the hospital because of chills, fever, and a "heaviness in his chest" of about four weeks' duration. The physical examination was negative.

Roentgenograms of the chest showed well-rounded mediastinal masses of increased density along the trachea and the main bronchi.

Laboratory studies during the course of hospitalization showed total erythrocyte counts varying between 4.5 and 5 million. The total leukocyte count varied between 4,000 and 8,750 cells per cu. mm. The differential smears showed from 1 to 21 per cent eosinophils and averaged between 10 and 15 per cent. The lymphocytes varied from 12 to 24 per cent and the monocytes varied from 1 to 3 per cent. The urine was normal. The erythrocyte sedimentation rate was 38 mm. on admission and later dropped to 22 mm. per hour (corrected). The serum protein on admission was 7.2 Gm. per 100 cc. with 4.1 Gm. of globulin and 3.1 Gm. of albumin. Eight months after admission the total protein was 6.5 Gm. per 100 cc. with 5 Gm. of albumin and 1.6 Gm. of globulin. Twelve months after admission the total protein was 6.8 Gm. per 100 cc. with 3.6 Gm. of albumin and 3.2 Gm. of globulin. A serologic test for syphilis (Kahn), the skin reaction to tuberculin, and complement fixation test for coccidioidomycosis were all negative.

Serial roentgenologic studies of the chest on admission revealed marked enlargement of the mediastinal nodes and a fibronodular infiltration in both lower lung fields. The mediastinal nodes regressed slowly. The pulmonary infiltration showed marked fluctuation, first extending to involve also the upper portions of the lung fields, and later receding with resultant clearing of the left lung field. After a period of regression, new areas of infiltration developed in the hilar zones; the infiltration was of fibrous character. Cardiac enlargement on the right could also be observed. An electrocardiogram showed ST_1 depression of 2 mm. with inversion of T_2 and T_3 and right-axis deviation. The exacerbation of the pulmonary involvement was again followed by a significant remission after eighteen months. The left mediastinal nodes became reduced to almost normal size. The electrocardiogram returned to normal, but maintained a right-axis pattern.

Tissue obtained by a biopsy of a cervical lymph node showed changes characteristic of sarcoidosis.

Case 8: A 23-year-old male was admitted to an overseas hospital because of amoebic infection and a "loose," productive cough. Physical examination revealed a generalized lymphadenopathy. The patient was successfully treated for amoebiasis with emetine and diodoquin, and returned to the United States because of the lymphadenopathy.

Physical examination upon admission revealed enlargement of the posterior cervical nodes. Both upper eyelids were swollen; the lacrimal glands were involved.

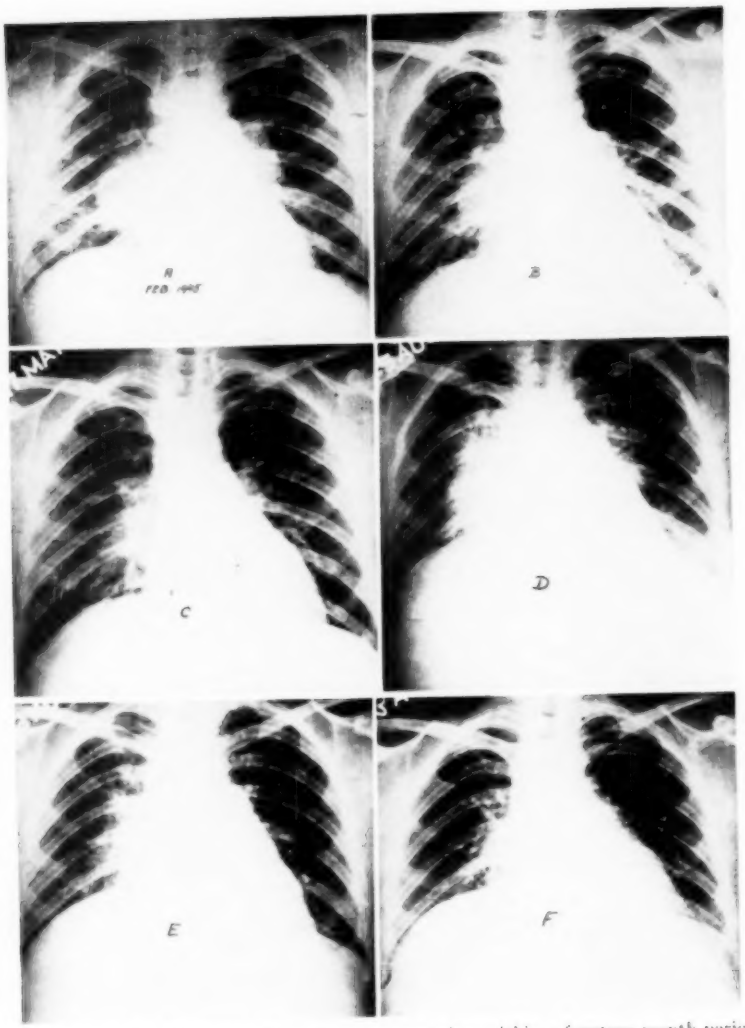

FIG. 8. Case 7. A-F. Series of roentgenograms taken within a fourteen-month period, showing the fluctuating character of the disease with regressions and exacerbations and a change of the cardiac shadow suggestive of cor pulmonale.

Laboratory findings showed normal values for total erythrocyte and leukocyte counts. The erythrocyte sedimentation rate was 15 mm. per hour. The values for serum protein, calcium, and phosphorus were all normal. The skin reaction to tuberculin was negative.

Roentgenographic examination of the chest showed slight prominence of the lung roots.

a fairly diffuse peribronchial fibrous infiltration in both inner zones of the lung fields, and a miliary nodulation in both bases.

Hospital course: The edema of the eyelids and lacrimal glands subsided after three weeks, without recurrence. Roentgenographic examination of the chest three months later revealed no evidence of mediastinal adenopathy. However, increased infiltration was present in the parenchyma which showed nodular areas of increased density, many of which coalesced. In spite of this, the patient improved steadily and was entirely symptom free

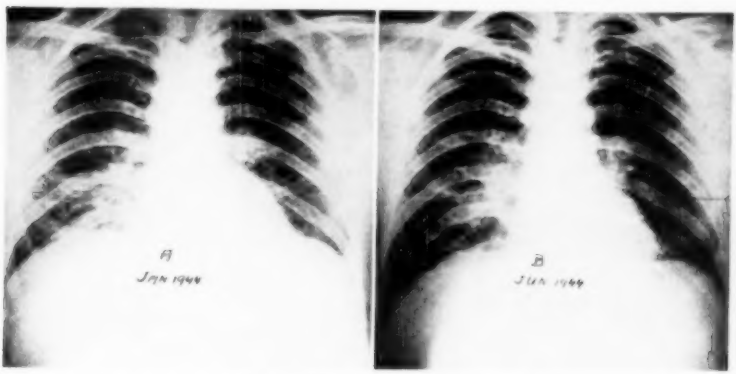

FIG. 9. Case 8. A. Mediastinal adenopathy and fibronodular parenchymal infiltration. B. Regression of the nodes, no improvement of the parenchyma, which showed coalescence of several groups of nodules into larger foci.

six months after admission. Roentgenographic examination at this time showed essentially no change of the disseminated nodular parenchymal infiltrations. Repeated biopsies from peripheral nodes were negative. The diagnosis was established histopathologically after a biopsy of one tonsil.

Cardiovascular Manifestations

Longcope (19) has emphasized the importance of extensive myocardial involvement as evidenced by clinical and electrocardiographic findings observed in about 10 per cent of cases. The clinical manifestations have been in the nature of arrhythmias, conduction defects, cardiac enlargement, paroxysmal tachycardia, and right-sided failure. The heart may be involved primarily by infiltration of the myocardium by the sarcoid granulomatous lesions. Even in the absence of direct cardiac involvement, a cor pulmonale may result from pulmonary vascular obstruction as a result of extensive pulmonary involvement.

Johnson and Jason (11) reported a patient with generalized sarcoidosis who died in congestive heart failure twelve days after admission to the hospital and only six months after the onset of his illness. Sarcoid lesions were demonstrated in the peri-, myo-, and endo-cardium. One patient in the present series showed right cardiac enlargement (Case 7) associated with depression of ST_1 and inversion of T_2 and T_3 with right-axis deviation.

Cardiac involvement was also demonstrated electrographically and clinically in the following cases:

CASE REPORTS

Case 9: A 25-year-old male was admitted because of malaise, shortness of breath, and multiple subcutaneous nodules which were identified histologically as sarcoidosis. Physical examination revealed a marked bradycardia with a pulse rate of 40. There was no evidence of congestive heart failure. The venous pressure was not elevated. The circulation time (arm to periphery), using calcium gluconate, was fifteen seconds. Roentgenographic examination of the chest showed enlarged mediastinal nodes and fibrous peribronchial infiltration of the pulmonary parenchyma. An electrocardiogram on admission showed a complete heart block with left-axis deviation and low T_1 and T_2 and inverted T_3. It was believed that the low T waves may have been a result either of the conduction disturbance or the presence of actual myocardial damage caused by sarcoid infiltration.

Six weeks later the auriculoventricular conduction had returned to normal except for a sinus arrhythmia. The T waves had increased in amplitude.

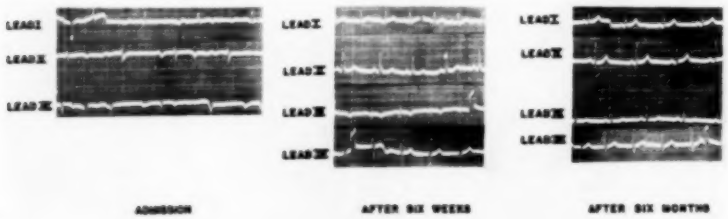

FIG. 10. Case 9. Electrocardiograms which on admission showed complete heart block, left-axis deviation, low T waves in leads I and II, and inversion of T_3. After six weeks the auriculoventricular conduction returned to normal and the T waves increased in amplitude. Further improvement was noted after 4 months.

After six months an increase in T waves was the only significant change from the previous tracing. Clinical recovery ensued after six months, and the patient was discharged from the hospital.

Case 10: A 19-year-old male was admitted because of palpitation, "racing" of the heart, and shortness of breath.

Roentgenographic examination of the chest showed enlarged hilar nodes and a moderate pleural effusion on the right which resorbed completely after eight months. Material obtained from a biopsy of a cervical node revealed sarcoidosis. An electrocardiogram revealed the picture of a shifting pacemaker with short runs of nodal rhythm, followed occasionally by a normal complex. This showed no significant change after four months.

Skeletal Manifestations

Jüngling (13) first described skeletal changes in sarcoidosis in 1919, referring to them as "osteitis tuberculosa cystoides." These osseous changes are said to occur in approximately 20 per cent of the cases (26), but were present in only 3 patients of the present series. The bone lesions, when present, are frequently so characteristic that they may be regarded as virtually pathognomonic of sarcoidosis. The lesions, resembling small cysts, are found in the phalanges of the

fingers and toes. Two main types of bone lesions have been described (26): a *circumscribed form* which consists of sharply defined "punched-out" areas of rarefaction, circular or oval in shape, usually located within the cancellous portion of the bone without evidence of bone reaction; and a *diffuse form* which produces a reticular appearance of the bone due to multiple small irregular areas of rarefaction. In this type, large portions of bone are usually involved, frequently resulting in alteration of its size and shape. The shaft is widened and the cortex is thinned out.

Less frequently, granulomatous involvement of the bone marrow has been demonstrated in spite of the absence of roentgenologically demonstrable bone alterations. Cases with diffuse osteoporosis, para-articular soft tissue swelling, and severe cartilage destruction are rare and are difficult to differentiate roentgenologically from rheumatoid arthritis (Case 11).

Clinical symptoms are not remarkable. Subjective symptoms such as pain are inconspicuous. Periarticular nodules have been observed frequently. These bone alterations seem to be more prevalent in the presence of cutaneous sarcoidosis (26).

CASE REPORTS

Case 11: A 30-year-old male was admitted because of abnormal chest findings detected during a mass roentgenologic screening, and consisted of mediastinal adenopathy and the fibrous type of parenchymal infiltration. There were no symptoms referable to the chest. He had noted some stiffness of the phalangeal joints of the hands and feet and slight swelling of these extremities. In the morning he could not close his hand completely. This improved with activity during the day.

Laboratory studies were unrevealing except for an erythrocyte sedimentation rate of 18 mm. per hour, and a differential leukocyte count showing 7 per cent eosinophils. Examination of biopsy material from a posterior cervical lymph node revealed sarcoidosis.

Roentgenographic examination of the hands showed diffuse osteoporosis of all bones. There was a marked narrowing of the radiocarpal and intercarpal joint spaces. The articular surfaces of the carpal bones were irregular, due to considerable bone destruction. The metacarpophalangeal and interphalangeal joint spaces were also narrowed. The articular surface of some metacarpal bones and phalanges was eroded.

Case 12: A 30-year-old male developed an acute upper respiratory infection, with afternoon temperature rises from 100° to 101 °F. from which he failed to recover satisfactorily. Physical examination on admission was essentially negative. However, a roentgenogram of the chest showed an enlargement of the mediastinal and paratracheal nodes and a rather extensive peribronchial infiltration in both lungs.

Laboratory studies: A total erythrocyte count was 4.6 million cells per cu. mm. The total leukocyte count was 7,800 cells per cu. mm. with a differential count of 8 per cent eosinophils, 57 per cent neutrophils, 32 per cent lymphocytes, and 3 per cent monocytes. The first-strength tuberculin test was negative, and the second-strength 2 plus. The erythrocyte sedimentation rate ranged between 35 and 50 mm. per hour. The values for the serum proteins, phosphorus, and calcium were all normal.

Hospital course: The pulmonary symptoms improved considerably after one month, and the temperature returned to normal. However, at this time the patient complained of vague, fleeting pains in all joints. Shortly thereafter the interphalangeal joints of the hands and feet became swollen. The motion within the affected joints was restricted. There was no significant inflammatory reaction of the overlying soft tissues. Roentgenographic

FIG. 11. Case 11. (Top) Roentgenogram of hand showing diffuse osteoporosis of all bones with narrowing of the radiocarpal, intercarpal, metacarpophalangeal and interphalangeal joint spaces. The articular surfaces of the phalangeal, carpal, and metacarpal bones were eroded.

FIG. 12. Case 12. (Bottom) Roentgenogram of the hands showing demineralization of the juxta-articular portions of the bones with erosion of the articular surfaces of the involved metacarpals and phalanges. Small cystic areas were present within the heads of several metacarpal bones as well as partial subluxation of some of the phalanges.

examination of the hands first showed moderate demineralization of the juxta-articular portions of the bones, followed later by marginal erosion of the articular surfaces of the involved metacarpals and phalanges. Small cystic areas of rarefaction were also present within the heads of several metacarpal bones. As the lesions grew progressively worse, par-

tial subluxations of the phalanges became apparent. The hands became grossly deformed. Almost simultaneously with the skeletal changes, small nodular lesions about 4 mm. in diameter appeared in the subcutaneous tissue. The nodules were widely spread, but were more numerous over the involved joints. The nails became brittle and showed pitting in many areas. Biopsy material from a skin lesion revealed sarcoidosis. The cutaneous manifestations subsided after about eighteen months without scar formation. Repeated roentgenographic studies of the chest showed a marked decrease in size of the mediastinal and paratracheal nodes, but the peribronchial infiltration was still present at the time of his discharge from the hospital. Roentgen therapy of the involved joints was ineffective.

Lymphatic System

The reticulo-endothelial system, particularly the lymphatic component, is almost universally involved in all cases of sarcoidosis at some time during the course of the disease. This seems to be true regardless of which visceral organs are the site of the disease. The intrathoracic adenopathy, which has been observed in about 85 per cent of the cases (26), has been previously discussed. Of the peripheral nodes, which are involved in about 75 per cent of cases, the cervical, axillary, and inguinal are most commonly affected. Epitrochlear and auricular adenopathy has been reported in about 50 per cent of the patients, but the incidence in the present series was considerably lower. It should be emphasized that the lymphadenopathy is systemic and is not limited to the regional lymphatics. This is true in spite of the fact that the distribution of the basic disorder within the lymphatic system is variable.

The enlarged lymph nodes are firm, rubbery, discrete, and nontender. They are not adherent to the surrounding tissues. Although sarcoidosis can frequently be demonstrated in nodes which are of normal size, large nodular masses which attain the size of a hen's egg are occasionally encountered. The involved nodes frequently undergo complete spontaneous regression. Following acute exacerbations, the nodes may reveal many areas of typical sarcoidosis which may not have been present during remission (Cases 1, 5, 6, 13). The writers shared the experience of others (25) who found evidence of tonsillar involvement, although the peripheral nodes were normal on repeated biopsy studies. This has frequently proved valuable in confirming the clinical diagnosis, when lymphadenopathy or skin lesions were absent (Cases 2, 8).

Splenic involvement, as evidenced by enlargement, occurs in about 30 to 40 per cent of patients at some time during the course of the disease. At autopsy, an incidence of 80 per cent (22) has been noted. The splenomegaly is usually not marked. However, in one case reported in the literature splenectomy was indicated because of excessive splenomegaly (26).

Hepatic Manifestations

The liver is probably involved in this process during the disseminated phase of the disease. Although the literature records this only as an infrequent occurrence, it is believed that hepatomegaly is in no way a true indication of the incidence of hepatic involvement. For example, in the present series of 28 cases, an enlargement of the liver was noted in only 4 cases. When liver function tests were performed, however, abnormalities were demonstrated in 8 out of 12 cases

studied in the acute stage of dissemination. Retention of bromsulfalein was particularly consistent and significant. It is believed that liver damage due to sarcoid infiltration may be the basis of the reversal of the serum albumin-globulin ratio when it occurs in this disease. In the present series a remarkable increase in serum globulin was noted in not more than 20 per cent of the patients so that the frequency of such a reversal seems to have been overemphasized (6, 8). Of 6 patients upon whom liver biopsies were done during the acute phase of the dis-

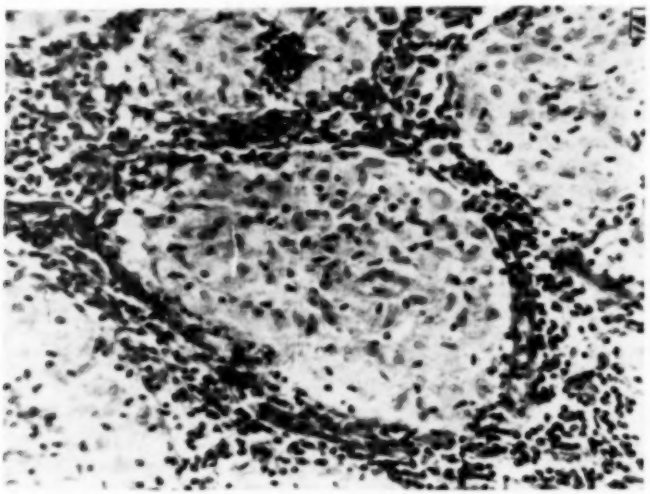

FIG. 13. Case 13. Microscopic section of a lymph node × 300 B.G.H. Acc. No. 3415.

ease, using the Vim-Silverman needle, sarcoid lesions were found in 5[2]. These findings support the belief that the incidence of liver involvement is probably high.

Positive findings on examination of material from liver biopsy established the clinical diagnosis in the following case, after repeated lymph node biopsies were inconclusive.

Case 13: A 26-year-old Negro male was admitted because of pain in the chest aggravated on deep inspiration, shortness of breath on exertion, and weakness. Physical examination was essentially negative except for enlarged posterior cervical, posterior auricular, and inguinal nodes varying in size from that of a pea to a walnut. They were firm, nontender, and freely movable.

Laboratory studies: Urinalysis revealed 1 plus to 2 plus albuminuria at various times during his hospitalization. The total erythrocyte count was 5.0 million cells per cu. mm.

[2] Since the preparation of this manuscript, one of us (J. H. M.) has had the opportunity to observe at the Philadelphia General Hospital 3 patients not included in the present series, with hepatic involvement as proved on liver biopsy. The only manifestations displayed by one of these, either clinically or from a laboratory viewpoint, were malaise, hepatomegaly, an abnormal retention of bromsulfalein, and disturbance of serum proteins to a minimal extent.

The total leukocyte count was 9,000 cells per cu. mm., with 5 per cent eosinophils. The erythrocyte sedimentation rate ranged between 10 and 60 mm. per hour over a six-month period. Sputum examinations were repeatedly negative for tubercle bacilli. The skin reaction to tuberculin was 1 plus in first strength and 4 plus in second strength. The icterus index one month after admission was 19. At the same time, the bromsulfalein test showed 42 per cent retention after forty-five minutes. The values for serum calcium and phosphorus were normal. The serum proteins were 7.5 Gm. per 100 cc. with 3.5 Gm. of albumin and 4.0 Gm. of globulin. A cephalin flocculation test was 2 plus at twenty-four hours and 4 plus at forty-eight hours. A serologic test for syphilis was positive on two occasions, but became negative after one month without treatment.

Hospital course: The patient was afebrile during the entire time of hospitalization. The chest pain and shortness of breath soon improved. The weakness persisted, however, and on several occasions the patient complained of epigastric tenderness. On one such occasion, the liver was enlarged about 4 cm. below the costal margin. The spleen was also enlarged on one occasion. The patient lost about 20 pounds of weight during the initial three months of observation, after which his weight remained constant. Repeated liver function tests showed evidence of hepatocellular damage. The patient improved gradually, and after three months 26 per cent bromsulfalein retention was present, which was reduced to only 12 per cent at the end of six months.

Roentgenographic examination of the chest revealed small nodular parenchymal infiltrations in both lung fields and large nodes in both hilar areas. Subsequently these nodes decreased in size, but the parenchymal lesions did not change significantly.

Repeated lymph node biopsies yielded material which was negative for sarcoidosis during the first three months. Liver biopsy material examined about that time revealed sarcoid lesions, which also were demonstrated later in the peripheral nodes.

The observations in this case emphasize the possible degree of liver damage in the stage of acute dissemination of sarcoidosis as it is reflected in liver function tests. The observations also demonstrate conclusively that tissue biopsies, other than lymphoid, may be of considerable value. The false positive serologic tests for syphilis observed in this case have been reported previously as an occasional manifestation of sarcoidosis.

Skin Manifestations

Although cutaneous lesions are of considerable aid in providing a clue to the diagnosis of sarcoidosis, they are not a consistent feature of the disease. A large percentage of patients never exhibit such changes. For example, Reisner (26) reported an incidence of 40 per cent, whereas only 4 patients (14 per cent) in the present series demonstrated skin involvement. The cutaneous lesions may be either nodular, or diffuse and plaque-like in character. In all instances of cutaneous involvement in the present series, the nodular type was present. The lesions also show individual differences, for some are cutaneous (lupus pernio), while others are subcutaneous (Darrier-Roussy subcutaneous sarcoid) (21). The lesions may be small and discrete (Case 12) or large (Case 4). Frequently more than one type of skin lesion is present in the same patient. The small nodular, large nodular, and the diffuse, plaque-like lesions may occur together in all possible combinations. The skin changes are disseminated in character and usually somewhat symmetrical in distribution. They tend to occur on the lateral surfaces of the extremities, face, chest, and abdomen, and over areas of osseous involvement.

They follow a course similar to pulmonary sarcoidosis, progressing in some areas, regressing in others; while in some lesions both phases may be encountered simultaneously. Complete regression occurs in about 50 per cent of the patients (26). Healing, when it does take place, is usually complete and there are no residual scars. In an occasional case, however, atrophic scars result. Dystrophic nail changes have been noted (Case 12). The coexistence of typical sarcoid lesions with skin tuberculosis, suggesting a transition from one disease (sarcoidosis) to the other (tuberculosis), has been reported. A similar transition has been observed in cases of pulmonary disease by Pinner (23).

One patient (Case 4) was somewhat exceptional in that the lesions, which were of the nodular subcutaneous variety, were quite large, measuring 5 to 7 cm. in diameter in many areas. They were distributed over the entire body, were nontender, and had the firm consistency of multiple subcutaneous fibromas. Examination of biopsy material from these lesions showed the typical histologic changes of sarcoidosis.

Parotid Gland Manifestations

The subject of salivary gland sarcoidosis is adequately presented in the literature and, therefore, needs only a brief mention here. The parotid gland may represent the only site of disease, but it is more frequently associated with involvement of the eye. Uveoparotid fever, a well-known syndrome produced by sarcoidosis, is the usual designation of the disease when the uveal tract and the parotid gland are involved. The combined disease of the parotid gland and the lacrimal duct exhibits the characteristics of the Mikulicz syndrome. Usually both parotid glands are affected and show a moderate, nontender, noninflammatory swelling. This is frequently accompanied by auricular adenopathy, and may result in facial paralysis due to involvement of the facial nerve as it passes through the parotid gland (16). The systemic manifestations accompanying this syndrome are often quite severe. The usual symptoms are malaise, weakness, fever, and weight loss. Clinical involvement of the parotid gland was noted in only 3 cases in the present series.

Eye Manifestations

Ocular manifestations of sarcoidosis have been reported in 25 to 50 per cent of cases (2, 26) and were present in 5 cases in the present series. The ocular lesions are frequently associated with parotid gland involvement. Ocular lesions are recognized today, however, as only a part of the systemic manifestations of sarcoidosis. If the ocular lesions are studied and followed, they are usually found to be associated with visceral lesions. Any part of the eye may be affected, although the most frequently involved structure is the uveal tract in the form of iridocyclitis. Bilateral granulomatous iritis, which causes little pain or redness, is not uncommon. Ciliary injection of varying degrees is usually present. The iris may become vascularized and nodules are frequently present on the pupillary border. Leukocytes are present in the aqueous humor. Heavy lardaceous deposits appear on the posterior surface of the cornea. The iritis is usually chronic, but

tends to heal with a minimum of permanent damage (21). Vitreous and corneal opacities, synechiae, and secondary cataracts are occasionally seen.

Tuberculous iridocyclitis and iridocyclitis due to sarcoidosis may appear almost identical, with small nodules on the iris, cloudy media, precipitates on the posterior surface of the cornea, and a tendency to form synechiae and cataracts. Boeck's sarcoid is usually less painful, however, and is less destructive and less proliferative. Tuberculous nodules have a dirty-white, smooth surface and are oval. The vessels tend to go around the nodules. When they resolve, atrophy of the iris results. In sarcoidosis, the vessels appear to enter directly into the nodules, which are larger and irregular (2). They tend to heal spontaneously without residuals. However, a satisfactory differential diagnosis frequently depends on other manifestations of the disease. Chorioretinitis has been reported and is usually seen with iridocyclitis. This was noted in one case (Case 1). Along with the typical iridocyclitis due to sarcoidosis, there was marked hyperemia of the disc. The retinal veins were engorged, and numerous small, flame-shaped hemorrhages were noticed around the periphery of the retina. The history of uveitis in this case extended over fifteen years.

In occasional cases the cornea, conjunctiva, or the lacrimal glands may be involved alone. The process is usually bilateral. The lacrimal glands were involved in one case (Case 8). In another patient chronic conjunctivitis was noted, which cleared spontaneously after two months. A third patient (Case 4) had moderate conjunctivitis with hypertrophy of both conjunctivae, ptosis of the eyelids, and involvement of the lacrimal glands. These improved gradually and appeared to have healed eight months later.

The clinical course of the ocular lesions is variable. Many cases, especially those in which the disease is limited to areas other than the uveal tract or only to parts of the uveal tract, may undergo complete regression. A few may progress to total blindness, particularly when the entire uveal tract is involved.

Nervous System Manifestations

Central nervous system involvement may include the brain and meninges (21). This is particularly seen in conjunction with involvement of the eye and parotid gland. Optic atrophy reported in one case (2) accompanied a cerebral lesion. Polyneuritis with transient paralysis occurs occasionally and apparently affects any of the cranial or peripheral nerves. Pituitary sarcoid reported in one case (17) produced signs of complete hypopituitarism.

Other Visceral Manifestations

Involvement of serous membranes manifested by pleural effusion or ascites has been noted occasionally in sarcoidosis. In the present series, pleural effusion was observed in one case (Case 10) together with electrocardiographic changes without evidence of cardiac failure. Mucous membrane involvement, which is usually limited to the respiratory tract, has been reported in 10 per cent of cases (26). This, as well as sarcoid of the thyroid, pancreas, kidneys, adrenals, epididymis, testes, or peripheral muscles which have been reported, did not occur in our patients insofar as we could determine.

PATHOLOGY

The final diagnosis of sarcoidosis rests on the histologic examination of involved tissue. The lesions have been described as miliary, tubercle-like lesions without caseation and without exudation. There is an accumulation of pale-staining, large polygonal epithelioid cells, frequently surrounded by a layer of lymphocytes which may also be scattered among the epithelioid cells (figures 5 and 13). Within the epithelioid follicles, occasional very large giant cells of the Langerhans' type are present, which contain peculiar inclusion bodies which stain with hematoxylin. Although single epithelioid cells may show slight necrobiotic changes, necrosis in the nodule is usually not observed. Between these nodules there is little fibrosis. There is no peripheral inflammatory zone about the nodule. The lymphocytes are more numerous in the early lesions during the phase of dissemination and less numerous during the chronic phase. These tubercle-like lesions do not increase in size, but increase in number so that eventually they give rise to shiny, pearly-gray masses easily visible to the naked eye (22). When the lesions regress, there is a tendency to fibrosis and hyalinization.

Pinner and Rubin (27), in a review of the literature and tissue sections from autopsied cases, were able, contrary to previous concepts, to find small amounts of caseation in a great number of cases of sarcoidosis. They were unable to recover tubercle bacilli from typical sarcoid lesions, yet in sections throughout the caseated foci the organisms were frequently present. The more caseation present, the more frequently was there a tendency to find tubercle bacilli. The bacilli could frequently be demonstrated only on animal subinoculation of the tissue. Histologic evidence of the gradual transition of sarcoid lesions to frank caseous tuberculous lesions was frequently observed. Therefore, small amounts of caseation cannot be accepted as conclusive proof against the diagnosis of sarcoidosis. Pinner and Rubin further pointed out that the inability to find tubercle bacilli in sarcoid lesions is not proof against the tuberculous etiology, since it is frequently impossible to demonstrate the organisms in subsiding or healed primary tuberculous lesions. Whether this presence of caseation is evidence in favor of the tuberculous background of sarcoid or whether it indicates secondary tuberculous infection depends largely on the interpreter's views. However, additional reports in the literature seem to weigh the evidence in favor of the tuberculous etiology of sarcoidosis (7, 23, 26, 27). For instance, Dorgeloh and Tully (7) reported a case of tuberculous lymphadenitis from which the organisms were obtained; at the same time the patient had typical sarcoid lesions of the overlying skin. The tuberculin reaction was negative. Reisner (26) reported a case which displayed typical sarcoid of bone and skin and which, in addition, showed adjacent tuberculous skin lesions from which the organisms were cultured. Johnson and Jason (11) report typical sarcoidosis of the heart from which tubercle bacilli were recovered on animal inoculation. It has been noted that, when tubercle bacilli are injected into the skin of rats, typical sarcoid lesions develop after ten days, yet the bacilli which were obtainable several days after injection were rarely obtainable by the time the skin lesions developed. The tuberculin tests in these animals may remain negative. Furthermore, BCG does not produce an

allergic skin reaction in patients with sarcoidosis as it does in normal individuals. Katz (14), on the other hand, has stated that tubercle bacilli cannot be cultured from sarcoid lesions; and Harrell (9) is of the opinion that sarcoid lesions merely represent a nonspecific, allergic response to the lipid fraction of a single organism or of a variety of organisms. Regardless of the etiology, about 15 to 20 per cent of patients with sarcoidosis die of tuberculosis (26). As these patients develop frank tuberculosis, any existing anergic response to tuberculin is reversed.

Reisner (26) and Katz (14) found tuberculin anergy in about 60 per cent of individuals with sarcoidosis, using dilutions of Old Tuberculin up to 1:100. In patients who did react, the reaction was not marked. This falls below the figure for the general population. The percentage of patients in the present series with anergy to PPD was only 40 per cent, which is not far removed from the general population.

Pinner and Rubin (27) previously were unable to demonstrate that anticutins played any role in the immunology of sarcoidosis. They found both procutins and anticutins in normal, tuberculous, and sarcoid patients. Therefore, blood procutin and anticutin studies were not investigated in this series.

It was not possible to demonstrate changes of serum phosphatase, calcium, or phosphorus in patients of the present series, although such changes have been reported by others (18, 21). Three patients in the writers' series did develop false positive serologic tests for syphilis; one as high as 40 Kahn units (Case 13). After several months the tests spontaneously reverted to negative in all 3 patients.

A reversal of the serum albumin-globulin ratio was present in approximately 20 per cent of the cases in this series. This is usually seen during the phase of generalization. The writers believe that it may be due to the high incidence of hepatic involvement during this phase, and that it has the same significance as any hepatocellular damage. It must also be remembered, however, that in practically all cases the reticuloendothelial system, particularly the lymphatic component, is involved, which may be reflected in an elevated serum globulin. Certainly fractionated globulin studies are indicated.

The erythrocyte sedimentation rate is almost always elevated. This is also particularly marked during the phase of dissemination.

The total leukocyte count is usually normal except for an occasional eosinophilia (21). Eosinophilia ranging between 5 and 20 per cent of the peripheral leukocytes was noted in approximately 25 per cent of the patients in the present series. In spite of repeated blood counts, it was not possible to substantiate the findings of monocytosis which Reisner (26) observed in 50 per cent of patients with sarcoidosis.

DIAGNOSIS

Polysystemic manifestations of the disease aid materially in arriving at a correct clinical diagnosis. For example, lymphadenopathy associated with asymptomatic parenchymal disease of the lung or characteristic skin and skeletal lesions are almost invariably recognizable as sarcoidosis. The ultimate proof, however, is provided by histologic examination of involved tissue.

In pulmonary sarcoidosis with mediastinal adenopathy, the great differential problem is Hodgkin's disease. The patient with Hodgkin's disease, once pulmonary manifestations are in evidence, rarely develops a spontaneous remission so characteristic of sarcoidosis. Patients with this type of Hodgkin's disease are usually quite sick. Roentgen therapy may cause a regression of Hodgkin's disease, but not of sarcoidosis. However, a concomitant spontaneous remission in sarcoidosis must be guarded against in the interpretation of response to roentgen therapy. Pulmonary involvement concomitant with mediastinal and tracheobronchial lymph gland involvement is much more common in sarcoidosis than in Hodgkin's disease.

Disseminated tuberculosis may offer considerable diagnostic difficulty, but today this is usually no great problem. The patient is usually less sick and the adenopathy more marked in sarcoidosis. Here a negative tuberculin test may be of great aid. Silicosis, lymphatic pulmonary carcinomatosis, pulmonary congestion, lymphosarcoma, leukemia, erythema nodosum, syphilis, fungus infection, and bronchiolitis should be considered and efforts made to exclude their presence.

TREATMENT

There is no known specific treatment for sarcoidosis. However, supportive therapy adds considerably to recovery. In the writers' opinion, bed rest is indicated during the acute phases. As the state of remission and chronicity is reached, the patient may be allowed increasing activity, not unlike patients with pulmonary tuberculosis, and gradually be returned to full activity. Regular periodic follow-up examinations seem to be indicated.

Although roentgen therapy has been reported as beneficial (24), it enjoys very little popularity today. Arsenic, tuberculin, leprosal, iodides, gold salts, fever therapy, and ultraviolet irradiation have all been tried and discarded. Streptomycin has recently been tried without apparent beneficial results (30).

SUMMARY

1. A clinical and roentgenologic study of 28 cases of sarcoidosis has been presented.

2. The fluctuating course of the disease, characterized by acute phases of generalization and remission (phase of visceral localization and chronicity), has been emphasized.

3. There seems to be little correlation between the clinical symptoms and the extent of organic disease. Pulmonary or mediastinal sarcoidosis may be entirely asymptomatic.

4. Sarcoid lesions of the cardiovascular system are not easily recognizable. The electrocardiographic changes observed in 3 cases were suggestive of cardiac involvement.

5. Sarcoid lesions of bone may in some instances exhibit roentgenologic changes indistinguishable from rheumatoid arthritis.

6. The liver is frequently involved, as proved by biopsies and liver function tests.

7. A definite diagnosis of sarcoidosis can be established only by a biopsy.

8. There is some evidence to support the view that sarcoidosis is related to tuberculosis. However, only one case in this group of 28 cases was proved to have active tuberculosis.

SUMARIO

Sarcoidosis. Estudio Clínico y Roentgenológico de 28 Casos

1. Este estudio clínico y roentgenológico comprende 28 casos de sarcoidosis.

2. Recálcase la evolución fluctuante de la enfermedad, caracterizada por fases agudas de generalización y remisión (fase esta de localización en ciertos órganos y cronicidad).

3. Parece haber poca correlación entre los síntomas y la extensión de la enfermedad orgánica. La sarcoidosis pulmonar o mediastínica puede ser absolutamente asintomática.

4. Las lesiones sarcoideas del aparato cardiovascular no son fáciles de reconocer. Las alteraciones electrocardiográficas observadas en 3 casos eran indicativas de afección cardíaca.

5. En algunos casos, las lesiones sarcoideas de los huesos pueden manifestar alteraciones roentgenológicas indistinguibles de las de la artritis reumatoidea.

6. El hígado se halla frecuentemente afectado, según demuestran las biopsias y las pruebas de la función hepática.

7. Un diagnóstico preciso de sarcoidosis sólo puede establecerse con una biopsia.

8. Algunos datos apoyan la opinión de que la sarcoidosis guarda cierta relación con la tuberculosis.

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PNEUMOPERITONEUM WITH PHRENIC PARALYSIS FOR PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

Since the induction of the first artificial pneumothorax the procedure has been attended and sharply limited by the disease complications it produces. It has been said that he who induces lung collapse should be aware and capable of managing all the complications attending such collapse, but it appears that pneumothorax has produced a large volume of pleural empyemata for which in most cases there seems to be no satisfactory method of management.

Pneumothorax has been the most extensively used collapse method for pulmonary tuberculosis for a number of years. Because of the numerous well-known complications (empyema, which occurs in 10 to 40 per cent of pneumothorax cases [Rubin], varying directly with the extent of the disease; bronchopleural fistula; and so-called unexpandable lung), it seems obvious that sharper limitations must be placed on the use of this form of collapse therapy. The time and effort spent solely in treating the morbid complications of any therapeutic procedure are, in a sense, wasted and too much damage has been done in the past with injudicious pneumothorax. It would seem that the time has arrived when it is inexcusable to ignore these well-known dangers associated with the procedure.

During the past eighteen years there has been a growing interest in the use of pneumoperitoneum to establish pulmonary collapse (2, 20, 39, 40). Significant numbers of patients have been treated during the past ten years and it has only been during the course of the last five years that long-range, more critical, and statistically significant communications have appeared in the literature (1, 17, 25, 29, 31, 37, 43). It is now a reasonable certainty that pneumoperitoneum, particularly when accompanied by phrenic paralysis, offers a means of effectively treating the hazardous pneumothorax group in addition to being useful in the more extensive disease group for which pneumothorax could never be considered. At the Clark County Tuberculosis Sanatorium, phrenic paralysis with pneumoperitoneum is used in all suitable cases, except in most of the minimal and certain early moderately advanced pulmonary lesions where pneumothorax has a safe effective range of therapy. Moreover, if pneumothorax collapse appears ineffective after three months, it is immediately discontinued and replaced by a phrenic paralysis and pneumoperitoneum (table 1). On this service the present ratio of pneumoperitoneum to pneumothorax is 6 to 1. Since this policy has been adopted there have been no new cases of tuberculous empyema, bronchopleural fistula, or unexpandable lung. Unlike pneumothorax, pneumoperitoneum, even though ineffective, is relatively harmless. It is easy and safe to induce and maintain and

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is most effective in controlling the disease, especially in the mid and lower lung fields, where pneumothorax is contraindicated.

The 100 cases presented in this series are consecutive and all have had phrenic paralysis with pneumoperitoneum. The early experience here at the Clark County Tuberculosis Sanatorium and the experience of others (7, 16, 32, 33, 34, 38) leads to the conclusion that a superior degree of effective collapse in pneumoperitoneum can be obtained with phrenic paralysis without increasing the risk of the whole procedure or introducing untoward long-range sequelae.

PROCEDURE

Much has been written about the method of peritoneal puncture (3, 11, 26) both for diagnostic and therapeutic pneumoperitoneum. Each clinician has developed a technique which he considers best for protracted use. The writers

TABLE 1

The Results of Phrenic Paralysis with Pneumoperitoneum as a Primary Collapse and Secondary to Ineffective Pneumothorax in the Treatment of Pulmonary Tuberculosis

STAGE OF TUBERCULOSIS	TOTAL PATIENTS TREATED	PATIENTS GIVEN PRIMARY PNEUMOPERITONEUM		PATIENTS GIVEN PNEUMOPERITONEUM AFTER PNEUMOTHORAX FAILURES	
		Number	Failures	Number	Pneumoperitoneum failures
All stages	100	43	17	57	4
Minimal	11	3	—	8	—
Moderately advanced	38	11	2 (1 dead)	27	4
Far advanced	51	29	15 (4 dead)	22	—

believe that the technique is of paramount importance in avoiding the complications which result directly from the manipulations involved.

For the initial administration of peritoneal air any anterior adbominal site may be selected except the right upper quadrant. Here one may accidentally embed the needle point in the liver substance. Air administered into the liver will result in air embolism, one fatal case having been reported by Mitchell (29) in 1947. In his early work Banyai (6) selected the eleventh intercostal space but he subsequently reported an undue number of instances of mediastinal emphysema. If the location of injections is changed to the anterior abdominal wall, this complication is virtually eliminated. The site of choice is the left upper quadrant about three finger-breadths below the inferior costal margin and at the lateral margin of the rectus, where the abdominal wall is thin and firm. Under this area the hollow viscera are quite mobile and the only solid viscus, the spleen, is well down in the peritoneal space.

An intracutaneous wheal of 2 per cent novocaine is raised and down through it a channel perpendicular to the plane of the abdomen at the site of injection is infiltrated from the skin through the peritoneum with 2 per cent novocaine. For air injection a three-inch, 15-gauge Potter-Kirschner side-eye needle is used. Since this needle has a relatively dull, trocar point, twisting pressure is required to penetrate the skin. After skin penetration the needle usually glides through the underlying tissue with ease and care should, therefore, be taken

so that sudden penetration does not occur. As the needle progresses from the subcutaneous tissue to the intra-abdominal space, two distinct layers of resistance are encountered, the aponeurosis and the peritoneum. Penetration is indicated by (*1*) the disappearance of resistance at the needle tip; (*2*) free, unrestricted lateral motion of the needle tip felt when the butt of the shank is displaced radially from the axis of penetration; and (*3*) free, almost effortless introduction of air with a well water-lubricated 2 cc. syringe. Repeated attempts at aspiration are made to ensure that the needle tip does not lie within a blood vessel. When the operator feels certain that peritoneal puncture is satisfactory, the needle butt is then attached to a Davidson pneumothorax apparatus. This equipment is used because positive pressure can be applied manually for the administration of air. Initially 10 to 20 cc. of air are allowed to run in by gravity water displacement. If the displacing water flows freely and no high pressure develops from this amount of air, 100 cc. of air are then permitted to flow into the peritoneal space, still implemented by gravity pressure. Manometric readings are again made and if no significant (plus 1 cm.) pressure develops, the total initial volume is then administered. The initial volume ranges between 400 and 1,500 cc. The guide to the volume of air required is the development of a low positive intra-abdominal pressure in the order of 4 to 6 cm. of water. In the average patient 1,000 cc. initially is well tolerated and produces a significant adequate pressure which facilitates the diaphragmatic rise. The needle is withdrawn and the puncture area covered with a small dressing.

The induction period, the time required to produce optimal intra-abdominal pressure to obtain adequate diaphragmatic rise, requires three to sixty days. The time is governed by the mobility and flaccidity of the diaphragm, the tonus of the abdominal musculature, the condition of the lungs and pleurae, and the ability of the patient to tolerate intraperitoneal air under pressure (9, 21, 36). During the first two weeks, which is the average length of time consumed in this induction period, air is administered every three days. Following this period, weekly injections of air are required to maintain adequate collapse. The volume of refills varies considerably in the same patient. Fluoroscopic examination before each refill should be used to determine the degree of collapse and the relative need for air. This observation combined with measurements of the intraperitoneal pressures serves as the guide for the injection volume. It can be observed that in the same patient the same intra-abdominal pressure will maintain the same approximate degree of collapse. In the writers' experience, it has been found that most patients will tolerate a positive 10 cm. of pressure. However, some people can accustom themselves to 16 cm. of pressure. In the majority of the patients of the present series, the pressures oscillate with respirations between 8 and 11 cm. of water after refill. The extremes of the range in this series lie between 4 and 16 cm. The volume required to produce these pressures averages about 800 to 1,200 cc. However, as little as 250 cc. and as much as 2,000 cc. of air have been given. In some instances, in order to maintain adequate pressures (22), an abdominal binder can be used with the added advantage of giving comfortable support to a protuberant abdomen and a more presentable cosmetic appearance.

Pneumoperitoneum is maintained for the same length of time as pneumothorax, that interval depending on the extent of disease and the progress of the patient.

RESULTS

In the 100 consecutive patients reported, 43 had unilateral and 57 bilateral tuberculosis; 16 of the latter had adequate pneumothorax on the side contralateral to the paralyzed hemidiaphragm. In 39 of the cases with bilateral disease, no contralateral collapse was present, as the phrenic paralysis had been executed on the more extensively involved side. In 42 of these 100 patients pneumothorax had failed because of extensive adhesions. No patients are included who have

not been followed for at least three months after the establishment of adequate pneumoperitoneum with phrenic paralysis. In the minimal group the interval of observation ranges between nine and thirty-six months, the mean being twenty-four months. In the moderately advanced group, the minimum observation time was four months in 2 cases, nine months in 2 cases, and the remainder ranged between twelve and forty-eight months, the mean being 20 months. In the far advanced group 5 cases were observed between four and ten months, the remainder between twelve and sixty months, with the mean located at twenty-four months.

TABLE 2

Results of Treatment in 100 Cases of Pulmonary Tuberculosis Classified According to the Stage of Disease

	11 MINIMAL		38 MODERATELY ADVANCED		51 FAR ADVANCED	
	Satisfactory results	Failures	Satisfactory results	Failures	Satisfactory results	Failures
Arrested	10		15		12	
Apparently arrested			7		6	
Quiescent			5		2	
Improved	1		4		12	
Unimproved				6		15
Dead				1		4
Total	11, or 100%		31, or 82%	7, or 18%	32, or 63%	19, or 27%

In tabulating the results of this series three criteria have been used in evaluating the merit of the procedure:

1. General status classification according to Diagnostic Standards and Classification, National Tuberculosis Association, 1940
2. Cavity closure
3. "Sputum conversion"

In the entire series, 74 per cent of the patients were considered to have attained favorable results and in 26 per cent the procedure was considered to have been a failure. There have been 5 deaths in the series due to pulmonary tuberculosis. In each of the disease classifications the results are summarized in table 2.

Cavity Closure

The presence of cavity was determined by the visualization of the usual annular shadow on roentgenography, with confirmation at fluoroscopy, the shadow retaining its configuration when viewed at all angles.

In the entire series there were 52 patients with cavitation. Of these, 28, or 54 per cent, attained cavity closure during treatment. Table 3 summarizes cavity closure in each of the three disease classifications. Seventeen, or 61 per cent, of the cavities closed during the second, third, and fourth months of treatment. Three closed during the first month and eight closed between the fifth and the sixteenth months.

"Sputum Conversion"

In evaluating "sputum conversion" it is necessary to consider the status of a contralateral lung, Accordingly, the tabulation (table 4) is broken down into

TABLE 3

The Cavity Closures Classified according to Stage of Tuberculosis

STAGE OF DISEASE	TOTAL PATIENTS TREATED	CASES WITH CAVITATION			
		Number	Remaining open	Resulting in closure	
				Number	Per cent of cases with cavities
All stages	100	52	23	28	54
Minimal	11	—	—	—	—
Moderately advanced	38	17	3	13	81
Far advanced	51	35	20	15	43

TABLE 4

The Sputum "Conversion" of 100 Patients with Pulmonary Tuberculosis Classified as to Stage of Disease and the Presence of Cavitation

STAGE AND EXTENT OF DISEASE AND CAVITATION	TOTAL PATIENTS TREATED	PATIENTS WITH SPUTUM POSITIVE FOR *M. tuberculosis*		
		Total	"Conversions"	
			Number	Per cent of total
All stages	100	98	59	60
Minimal	11	9	9	100
Moderately advanced	38	38	28	74
Unilateral	22	22	19	86
Cavitation	9	9	7	78
No cavity	13	13	12	92
Bilateral	16	16	9	56
Cavitation	8	8	5	63
No cavity	8	8	4	50
Far advanced	51	51	22	43
Unilateral	10	10	3	30
Cavitation	6	6	2	33
No cavity	4	4	1	25
Bilateral	41	41	19	42
Cavitation	29	29	12	41
No cavity	12	12	7	58

unilateral and bilateral disease and further designation as to the presence or absence of cavitation is noted. In 59 of the 98 patients, smear of the sputum was negative for acid-fast bacilli for three months or longer and the result was confirmed by a negative culture.

In 36 of 98 patients, tubercle bacilli disappeared from the sputum during the first three months and this occurred in the greatest proportion during the first month of treatment. Tubercle bacilli disappeared from the sputum during the second three-month period in 13 patients; during the third three-month period in 3 patients; and in the fourth three-month period in 2 patients. In the remaining 4 patients, the sputum became negative for tubercle bacilli between thirteen and twenty-one months after the start of treatment.

Failures

Failures (table 5) in this series were designated on the basis of inability to "convert" the sputum, close the cavity, or improve the disease. The highest incidence occurred in a group of patients who could not tolerate the air because of abdominal discomfort, frank abdominal pain, and protracted nausea and vomiting with prolonged anorexia. Seven such patients showed such intolerance. Next

TABLE 5

26 Failures in the Pneumoperitoneum Treatment of Pulmonary Tuberculosis

Abdominal discomfort	7
Inadequate diaphragmatic rise	5
Spread of disease	4
Tuberculosis peritonitis	3
Fibroid disease	2
Peritoneal effusion	2
Uncooperative patient	2
Ineffective collapse	1

in the order of frequency as a cause of failure was inadequate diaphragmatic rise in spite of paralysis. It must be borne in mind, however, that in this group of patients pneumothorax had failed or could not be induced. Spread of disease, tuberculous peritonitis with concomitant pain and subsequent development of adhesions, fibroid disease, peritoneal effusion, uncooperative patients, and ineffective collapse in spite of apparently adequate diaphragmatic rise account for the remainder of the failures.

DISCUSSION

Following the initial injection of air, the patient may or may not have moderate difficulty in adjusting himself to the various sensations which are probably the result of reorganization of the abdominal viscera, moderate abdominal distention, and transmitted intrathoracic pressure changes. The most frequent and most annoying difficulty encountered by the patients is pain referred to the base of the neck as a response to central diaphragmatic irritation. This shoulder pain is noted on the side contralateral to the paralyzed phrenic nerve. It is usually worse on the right, probably because of tension in the falciform ligament as the liver pulls away from the diaphragm.

As the diaphragm begins to rise to satisfactory levels, an increase in the amount

of sputum and the frequency of coughing are first noticed. After the initial phase of air induction, the patient's appetite begins to improve. On roentgenographic examination, the area of greatest disease becomes more dense, while the unaffected portion of the lung retains the normal characteristic appearance of a well-ventilated normal lung tissue. The contraction of the disease is accompanied by resolution of some of the exudative areas and will progress until the area becomes quite fibrotic and sharply demarcated.

Cavity closure occurs for the most part during the second and third months of well-established pneumoperitoneum with a satisfactory pulmonary collapse. Not infrequently, however, cavities close during the first month of pneumoperitoneum treatment but occasionally one year to eighteen months may be required. The residuum resulting from cavity closure is presumably identical with that observed following any other form of collapse treatment. The size of the cavity and its location seem to be of little moment in regard to the possibility of its becoming closed by pneumoperitoneum. This phenomenon has been observed by Trimble and his co-workers in an analysis of 407 cases of pneumoperitoneum reported in 1948 (43). The explanation probably lies in the fact that pneumoperitoneum produces a uniform collapse of pulmonary tissue, allowing the diseased area, which is most contractile, to shrink selectively. It has been demonstrated that there is little long-range alteration in the pleural pressure (21) and that the collapse is due entirely to a significant uniform decrease in the pulmonary volume (4, 5, 8, 35). In view of these observations and the observations of others, the writers believe that the principal factor governing the closure of cavities in pneumoperitoneum is the character of the cavity wall and the surrounding disease. In agreement with other observers, it is believed that fibrotic disease (19) and stiff-walled cavities cannot be improved by this method (13, 17, 19, 25).

Since phrenic paralysis with pneumoperitoneum is considered to be essentially a unilateral collapse, sputum "conversion" is difficult to evaluate in the presence of bilateral disease. For this reason it is obvious that in bilateral pulmonary tuberculosis, sputum "conversion" is not of critical importance in evaluating the efficacy of the collapse.

Complications: From the experience in the present study it appears that phrenic paralysis with pneumoperitoneum offers a remarkably effective method of temporary collapse which is exceedingly free of serious and debilitating complications. Indeed, a review of more than 3,000 cases reported in the literature shows that there have been only 7 deaths attributable to this procedure and all of these have resulted from air embolism (24, 29, 34, 35, 40, 43, 44). Perforation of the hollow viscera, while emphasized in the literature as a potential hazard, has not occurred in the writers' series nor in the series of Trimble (43) or Mitchell (29). Furthermore, in the few cases reported there have been no serious effects or sequelae from this technical accident (30). The hazard of perforation is indeed minimal, as has been demonstrated experimentally by a number of workers (Jacobeus, Stockholm, 1910). After a series of attempts at perforation on cadavers, Jacobeus was of the opinion that perforation was virtually impossible.

Air embolism is undoubtedly the most serious complication which can result

from this procedure per se. There has been one instance in the present series of presumed air embolism, and the complication was not fatal. In comparison with the incidence of air embolism accompanying pneumothorax (27) and in evaluating the number of cases reported in the literature as resulting from pneumoperitoneum, it is safe to say that pneumoperitoneum offers a considerably smaller risk of air embolism. It is believed that this hazard can be virtually eliminated by careful technique and it is important that the operator be certain that the needle tip lies in a free space before the air is administered.

Tuberculous peritonitis seems to occur more frequently in patients receiving pneumoperitoneum. This complication is seen only in far advanced disease. If we are to accept the postulate expressed by Banyai, that far advanced pulmonary tuberculosis is accompanied by intestinal and potential peritoneal tuberculosis, it cannot be said that pneumoperitoneum is a direct agent in the production of peritonitis but is merely a factor tending to reveal the presence of the disease. It is possible that pneumoperitoneum prevents the formation of walled-off tubercles because the gut is separated from juxtaposition with the abdominal wall. This is the opinion of Rilance and Warring (34) in their observations of the increased incidence of acute appendicitis in patients with pneumoperitoneum as compared to that of a similar group in the same sanatorium population who did not receive pneumoperitoneum. If this be the case, then the designation of tuberculous peritonitis as a complication of pneumoperitoneum is a matter of opinion and viewpoint.

Sterile peritoneal effusions occur during the course of a small number of pneumoperitoneum treatments. Three such effusions occurred in the present series and in one it was not necessary to discontinue the pneumoperitoneum. Mitchell in 1947 and Trimble in 1948 had similar experiences in a larger series of cases. The reason for these transudates is obscure since Trimble and his co-workers (42) demonstrated at autopsy and subsequent microscopy that air produces little effect on the peritoneal serosa. They did observe, however, that a very mild chronic inflammatory reaction was present in a small number of cases. It is indeed possible and very likely that a small number of these peritoneal effusions, sterile in nature, result from idiosyncrasy of the peritoneum in its response to contact with air. It may be analogous to the transient, unexplained sterile effusions occurring in pneumothorax. Treatment of this complication consists in withdrawing as much air and fluid as necessary to keep the patient comfortable. As the fluid regresses and the diaphragm descends, instillations of air may be attempted. A deterrent factor which may develop is the formation of peritoneal adhesions producing pockets in which air may be trapped and, hence, may prevent the re-establishment of pneumoperitoneum.

Nausea and anorexia are benign complications which usually occur early in the establishment of adequate pneumoperitoneum. As the patient becomes adjusted to the air, this complication subsides (23). Persistent anorexia and nausea can usually be relieved by lowering the pressure within the peritoneal space. This may sacrifice the collapse in part. Nevertheless, as we must not lose sight of one of the essential factors in the treatment of pulmonary disease, namely,

adequate diet, a middle path must be selected. In the present series, 3 of 5 patients with prolonged nausea and anorexia were relieved by temporary lowering of the intra-abdominal pressure.

Aggravation of hernia and the development of latent hernia have occurred in this series as well as in the series of most other investigators of this form of collapse treatment. In the present series, the appearance of hernia necessitated the discontinuance of pneumoperitoneum in one instance, but the others were controlled by the lowering of pressures and the use of measures for external support. In all of these patients the disease continued to improve.

There are a number of other complications of pneumoperitoneum interspersed throughout the literature. Mediastinal emphysema occurred in a large number of Banyai's early patients (6), but was not observed in the present series. Other complications reported in the literature are: subcutaneous emphysema (20, 35, 66); retroperitoneal emphysema (35); pneumatocele; scrotal pneumatocele (30); peritoneal shock (25); atrophy of the diaphragm (1, 39); ruptured diaphragm (28); accidental pneumothorax (10, 35); diaphragmatic spasm, lobular atelectasis (39, 46); massive atelectasis (14); aggravation of hemoptysis (29); cardiac decompensation (18); and puncture of the inferior epigastric artery.

In view of the experience in the present series, it is believed that the following situations indicate the use of phrenic paralysis with pneumoperitoneum:

Failure of pneumothorax: Included under the designation of pneumothorax failure are tuberculous empyema and those cases in which pneumothorax could not be established.

Extensive disease: Even if pneumothorax can be induced in patients with extensive disease, it will undoubtedly be ineffective. Primary pneumoperitoneum with phrenic paralysis is indicated rather than subject the patient to a hazardous pneumothorax trial.

Large cavitation: Since large cavities usually extend to the edge of the lung and since there is little healthy lung tissue between the cavity wall and the visceral pleura, it is inviting trouble to initiate and maintain pneumorthorax in such a situation.

Bronchial disease: As the concentric type of collapse produced by pneumothorax tends to inhibit bronchial drainage and as it has been quite well demonstrated that pneumoperitoneum aids bronchial drainage, pneumothorax, if present, should be discontinued and pneumoperitoneum established as soon as the diagnosis of bronchial tuberculosis is made.

Basal disease with or without cavitation: Pneumothorax is of no avail and is indeed contraindicated in disease located at the base of the lungs. Good results have been seen in phrenic paralysis alone with this situation. The results following pneumoperitoneum have been most gratifying in the few cases of basal disease treated in the present series.

Other indications for pneumoperitoneum frequently listed in the literature, with which we agree in principle but have had no opportunity to observe, are: the postpartum state in order to maintain the collapse previously maintained by the fetus; and in old age, where the patient cannot tolerate pneumothorax and the degree of respiratory embarrassment it produces.

From the therapeutic failures and unsuccessful attempts to induce pneumoperitoneum experienced in the present study, it is believed that the following states contraindicate the establishment, or indicate the need for the termination, of pneumoperitoneum:

Moribund patients: The terminally ill patient is a respiratory cripple at the outset and needs all available lung tissue for respiratory function. In addition to the usual debility in such a patient, pneumoperitoneum is quite distressing and poorly tolerated.

Fixed diaphragm: Fluoroscopy, roentgenography, and spirometry serve as good indices of the diaphragmatic mobility in respiration. Nevertheless, these observations do not always predict the degree of rise that may be effected by the higher subdiaphragmatic pressures produced with pneumoperitoneum. It has been possible to move thick, apparently fixed hemidiaphragms in a number of empyema cases. It is probably good practice to initiate pneumoperitoneum first in an attempt to move the suspected fixed diaphragm. If rise is accomplished, paralysis will then add to the rise in most cases in the amount of one or two interspaces.

Fibroid disease with or without cavitation: Pneumoperitoneum is totally ineffective in cases which remain static in appearance, "positive" in sputum, and "open" in cavitation, in spite of high diaphragmatic rise and high intraperitoneal pressure.

Other concomitant diseases with poor prognosis: Examples of associated diseases which constitute contraindications for the use of pneumoperitoneum are silicosis, carcinoma, cardiac decompensation, and severe diabetes mellitus with its characteristic complications.

Low vital capacity: Pneumoperitoneum improves the vital capacity in some cases by bringing into tidal activity portions of the lung as yet not actively exchanging atmospheric gases. This is probably accomplished by allowing the diseased area to contract. As the pleural space retains its physiologically negative pressure, portions of the formerly passive lung are brought into activity. However, the variables are such that accurate prediction cannot be made.

Hernia: Hernias of abdominal origin which are overt will be made worse and adequate repair should be attempted before starting pneumoperitoneum.

Severe cardiac decompensation: Benatt and Berg demonstrated by electrocardiography an anti-clockwise rotation of the heart following pneumoperitoneum (12). This tends to embarrass the volume output and is conducive to ventricular fibrillation if the rotation is acute, which might occur with peritoneal air insufflations. While the writers have not had occasion to observe this, it is believed that severe heart disease contraindicates the use of pneumoperitoneum on the basis of known physiology.

SUMMARY AND CONCLUSIONS

The results of 100 consecutive cases of pneumoperitoneum with phrenic paralysis for pulmonary collapse have been presented, and the method of peritoneal air injection has been described.

In the entire series, a favorable result was observed in 74 cases. The results have been analyzed in terms of extent and status of disease, cavity closure, and sputum "conversion," and the data are presented in tabular form. The complications and therapeutic failures have been discussed and from these findings and the findings of others the following conclusions have been reached.

1. Pneumoperitoneum with phrenic paralysis as a single therapeutic instrument offers a safe, effective means of pulmonary collapse in those patients in whom pneumothorax is hazardous and contraindicated.

2. Pneumoperitoneum with phrenic paralysis offers collapse to the more extensively diseased patients who formerly could not have been considered for any type of collapse measure.

3. In contradistinction to pneumothorax, a collapse means is afforded by pneumoperitoneum which is easily and rapidly reversible and one which can be re-established in the event of reactivation.

4. Serious complications and sequelae are rare when pneumoperitoneum is correctly used.

5. Primary pneumoperitoneum with phrenic paralysis should be considered as a means in the management of some minimal and most moderately advanced and far advanced lesions of pulmonary tuberculosis.

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THE ELECTROCARDIOGRAM IN PNEUMOPERITONEUM

Including Augmented Unipolar Limb Leads and Unipolar Chest and Esophageal Leads

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The value of the electrocardiographic tracings taken with an electrode in the esophagus in various arrhythmias and tachycardias was demonstrated by Lieberson and Lieberson (1) and in subsequent studies by Brown (2), Luisada (3), and Butterworth and Poindexter (4). Hamilton and Nyboer (5) first used esophageal leads for localizing and evaluating posterior myocardial infarctions. Since then, Nyboer (6–8) and Myers and Oren (9) have used these leads more extensively for this purpose.

In the present studies an attempt was first made to study the effect on the electrocardiogram of the changes in the position of the heart produced by pneumothorax. The presence of air between various portions of the heart and the chest wall precluded accurate analysis of the effect of position alone. Conduction of electrical currents from the heart to the chest obviously had to occur through those portions in contact with each other. Because of this difficulty, patients receiving pneumoperitoneum were chosen for study. Although somewhat similar problems arose in these patients, they were less disturbing than was the case in patients with pneumothorax.

The effects of pneumoperitoneum, with and without phrenemphraxis, on the electrocardiogram have been described (10–14) but descriptions have been limited to the effects on the standard limb leads. The results obtained with esophageal and serial chest leads have not been described under these circumstances.

PLAN OF INVESTIGATION

Electrocardiographic studies were made in a group of tuberculous patients receiving pneumoperitoneum therapy at the Florida State Tuberculosis Sanatorium. Numerous unipolar chest leads anteriorly and posteriorly were obtained as well as unipolar esophageal and augmented unipolar limb leads and standard limb leads. There were 10 patients with pneumoperitoneum, 4 with left and 3 with right phrenemphraxis. Three esophageal tracings were taken with the patients in the upright position only, but seven were taken with the patients upright and recumbent and, in one instance, during different phases of respiration. With few exceptions, of the numerous chest leads taken, only the six unipolar precordial leads V_{1-6}, taken according to the technique of Wilson *et al.* (15–17), will be discussed in this paper. Goldberger's augmented unipolar technique (18 and 19), which is a modification of the unipolar extremity leads described by Wilson *et al.* (15), was used in taking the limb leads.

None of the 10 patients gave a history of having had rheumatic fever, hypertension, or heart disease, and there was no history of these in their families. No symptoms suggestive of coronary arterial disease were present. In every patient

the heart was thought to be normal on physical examination. All patients were males of slender build.

According to the criteria of Hamilton and Nyboer (5) and Nyboer (6 and 7), esophageal records with intrinsic auricular deflections (2) were assumed to have been taken from the auricular level EA and those with upright P waves from ventricular level EV. Esophageal leads were marked with the distance of the electrode from the nares in centimeters and with S or L, representing the sitting or lying position.

Q waves in the unipolar esophageal leads at the ventricular levels EV were considered abnormal if they were more than 4 mm. in amplitude according to the criterion of Nyboer (7) or over 25 per cent of the respective R wave as suggested by Myers and Oren (9).

OBSERVATIONS

Only one more or less characteristic case in each group is discussed in detail but the more important findings in the group as a whole are also included.

Representative Case Reports

Pneumoperitoneum with left phrenemphraxis

Case 1 (Figures 1 and 1A). W. D., age 21, had far advanced bilateral tuberculosis. Both sides of the diaphragm were high, especially the left. The heart was displaced upward and forward.

The right arm electrode „V_r faced the cavity of the right ventricle. The left leg tracing „V_f looked like $V_{5 \text{ and } 6}$, and the left arm tracing „V_l was of low amplitude and looked like chest lead V_2.

The heart apparently was in the semivertical position electrocardiographically.

With the patient in the horizontal position, prominent Q waves were present in esophageal leads at ventricular levels E47.5 to 40. Q waves increased in amplitude as the auricles were approached. T waves were inverted throughout. When the patient sat up, the Q waves decreased in amplitude.

It is possible that the left leaf of the diaphragm was between the esophageal electrode and the heart at the 45 cm. level but not the 40 cm. level.

Pneumoperitoneum with right phrenemphraxis

Case 6 (Figures 2 and 2A). C. C., age 23, had far advanced bilateral tuberculosis. Both sides of the diaphragm were high, especially the right. The heart was displaced upward, forward, and to the left. The electrocardiogram taken after treatment showed the axis to be normal. The left leg electrode faced the epicardial surface of the left ventricle; the left arm electrode, the epicardial surface of the right ventricle. QRS deflections in „V_l were small and looked like those in V_1; complexes in „V_f looked like those from the left side of the precordium. The heart was in the vertical to semi-vertical position. The precordial leads V_2' and $V_{2 \text{ and } 3}''$[1] suggested incomplete right bundle branch block.

The esophageal leads, taken in the sitting position only, showed abnormally large Q waves. The Q waves became larger as the upper ventricular border was approached.

The pneumoperitoneum was thought not to separate the heart and the esophageal electrode at the 40 cm. level.

[1] V_2' and $V_{2 \text{ and } 3}''$ were taken according to the nomenclature of Evans and Black (2). V_2' and V_2'' were taken at the left sternal border one and two interspaces, respectively, above the standard precordial lead V_2. V_3'' was taken at a point two levels above V_3.

Pneumoperitoneum without phrenemphraxis

Case 9 (Figures 3 and 3A). Patient J. C., age 42, had far advanced bilateral tuberculosis. Both sides of the diaphragm were elevated, the right slightly more than the left. The heart was displaced upward and forward. In the precordial leads there was only slight shift of the transitional zone to the left after treatment, but there were striking differences between

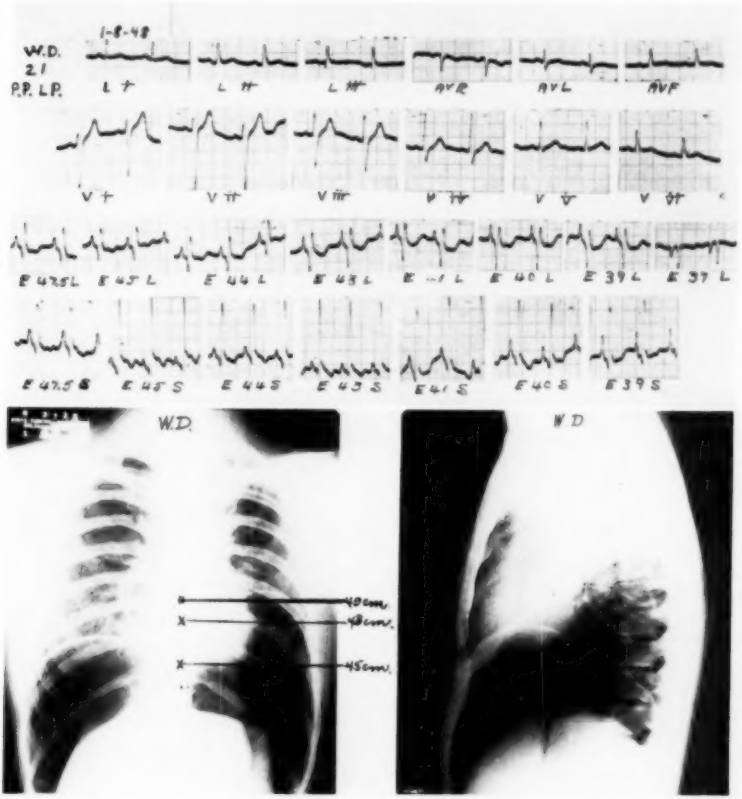

FIG. 1. (Top) Case 1, 21-year-old male. Pneumoperitoneum with left phrenemphraxis. Note prominent Q waves in esophageal leads at ventricular levels 40 to 47.5 cm. from nares.
FIG. 1A (Bottom) Same patient as figure 1.

the standard and unipolar limb leads before and after therapy. Before treatment these leads showed a semivertical heart without Q waves or abnormal axis deviation and after treatment a semihorizontal heart with moderate left axis deviation and abnormal Q waves in leads II, III, and aV_F. Q2 was 1 mm. and QRS 3 was in the form of a QS, 2.5 mm. in amplitude. Voltage in the standard leads was increased from 2.5 to 4 mm. The aV_L complex was changed from one consisting of an R wave measuring 2 mm. to a QR complex in which the Q and R measured one mm. each. Small Q waves appeared in V_6. T waves were upright

in all leads before and after treatment. Treatment apparently displaced the heart upward, rotated the heart counterclockwise on its long axis, and rotated the apex forward on the transverse axis.

Q waves were present at all ventricular levels in the esophageal leads, but did not exceed 4 mm. when the patient was recumbent. They were not normal, however, because the

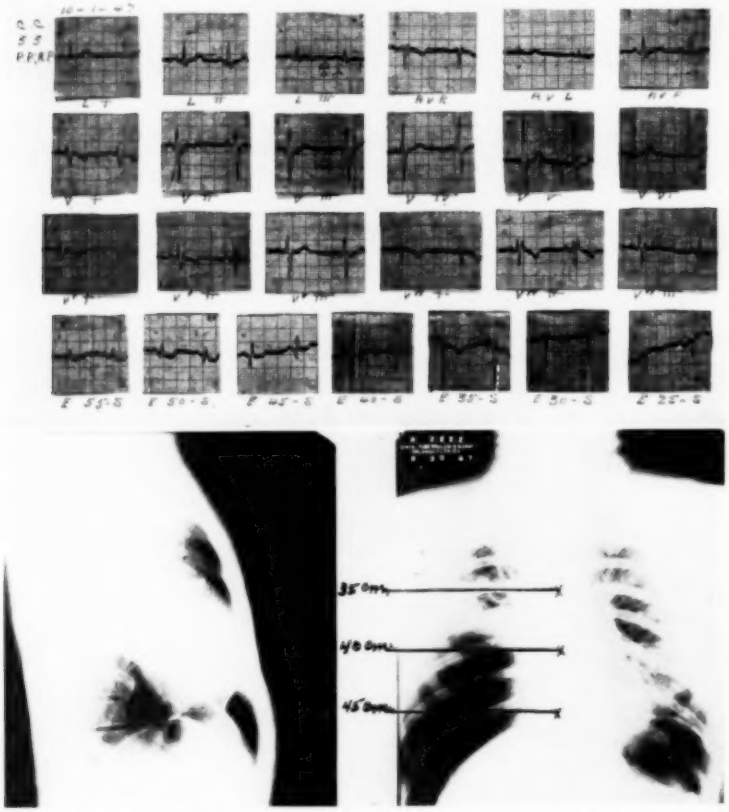

FIG. 2. (Top) Case 6. 23-year-old male. Pneumoperitoneum with right phrenemphraxis.
FIG. 2A. (Bottom) Same patient as figure 2.

Q R ratio was large, the Q wave reaching approximately 100 per cent of the R wave in E46L. The Q waves were generally larger in the sitting than in the recumbent position and the T waves were inverted in both positions. The amplitude of the Q waves increased as the electrode was placed nearer the auricular border.

The esophageal electrode was at the lower border of the heart at 45 cm. and centrally placed behind the heart at 40 cm. The diaphragm may have projected between the electrode and the heart at 45 cm. but not much above that level.

All precordial leads in the anteroposterior view appeared to be below the diaphragm.

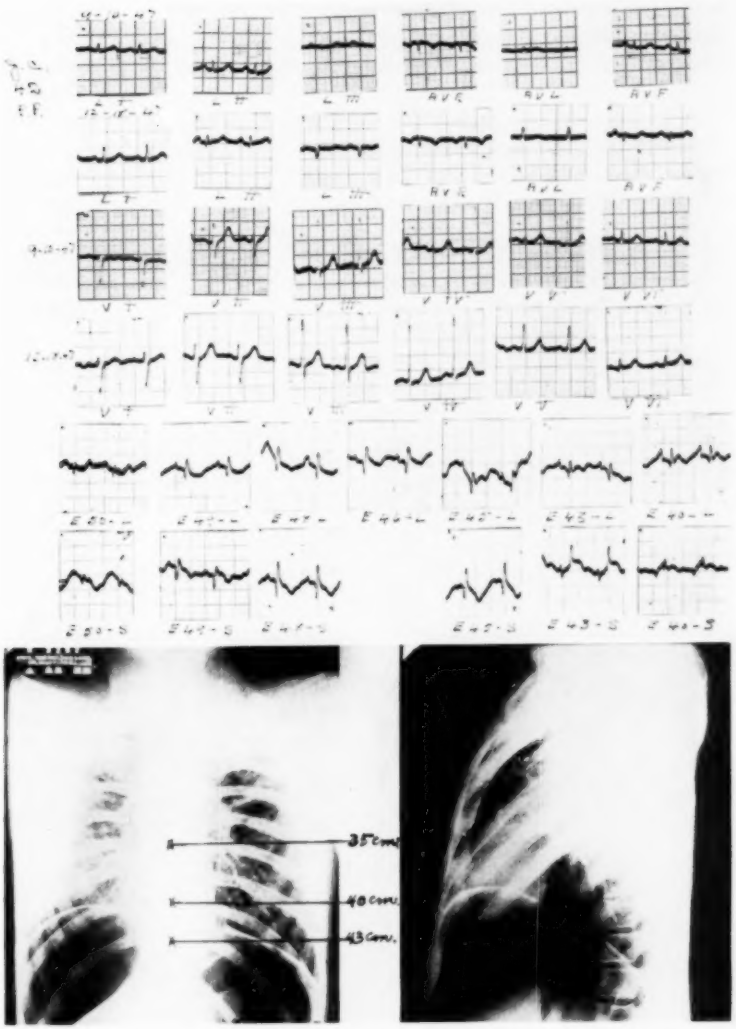

FIG. 3. (Top) Case 9. 2-year-old male. Pneumoperitoneum without phrenemphraxis. V_2' and V_2'' were taken at the left sternal border one and two interspaces above the standard precordial lead V_2, and V_2'' was taken at a point two interspaces above V_2 according to the nomenclature of Evans and Black.

FIG. 3A. (Bottom) Same patient as figure 3.

Summary of Findings in the Entire Group

Extensive electrocardiographic records and anteroposterior and lateral roentgenograms were obtained in all of the 10 tuberculous patients with pneumoperitoneum.

Roentgenograms showed that the heart was displaced upward and forward in all 10 patients studied. The displacement was to the right in one of 4 patients with left phrenemphraxis and to the left in all 3 patients with right phrenemphraxis and one of 3 patients with pneumoperitoneum without phrenemphraxis. In 3 of the 4 patients with left phrenemphraxis and 2 of the 3 patients with pneumoperitoneum only, no appreciable lateral displacement was noted.

Standard and augmented unipolar extremity leads and unipolar chest leads were taken with all patients recumbent, 7 after treatment and 3 before and after therapy. Esophageal leads were taken with the patients in the sitting and recumbent positions in 7 cases (during various phases of respiration in one), and in the sitting position only in 3 (one with left and 2 with right phrenemphraxis). Esophageal leads were taken after therapy only.

The standard and augmented unipolar limb leads and unipolar chest leads: Of the 4 patients with pneumoperitoneum and left phrenemphraxis, no abnormal Q waves were found in the standard, augmented unipolar limb or chest leads. Small Q waves were present in lead III in one case (figure 1) and in leads I and $_aV_L$ in another. There were only slight changes in the chest leads.

In the 3 patients with pneumoperitoneum and right phrenemphraxis, there was no abnormal axis deviation. Small Q waves were present in leads I and II in one case and in leads II, III, and $_aV_f$ in the other 2 (figure 2). Changes in the precordial leads were slight.

Of the 3 patients with pneumoperitoneum only, the precordial leads were taken before and after therapy in 2, but the standard and augmented unipolar extremity leads were taken before and after therapy in all. Abnormally large Q waves which were present in $_aV_L$ before treatment in one case were reduced. Abnormally large Q waves were formed in leads II, III, and $_aV_f$, leads in which there were no Q waves before treatment, in another (figure 3). Voltage was low in the standard and unipolar limb leads in this case. The electrical axis was shifted to the left in all 3 cases, to slight left axis deviation in one of these. The transitional zone shifted slightly to the right in one of 2 cases in which the precordial leads were taken before and after treatment 2 and slightly to the right in the other.

Esophageal leads: Abnormally large Q waves were present in the esophageal leads at ventricular levels after treatment in all 10 cases. The abnormally large Q waves were present: in all 3 cases in which records were taken in the upright position only; in recumbency in all 7 cases in which esophageal tracings were taken with the patient sitting and recumbent; and in the sitting position in 6 of the 7 cases. In the one case in which the Q waves were not abnormal with the patient sitting, assumption of the upright position caused the Q waves to become smaller although the total voltage (Q plus R) became greater. In general, the assumption of the upright position not only caused an increase in total

voltage, but an absolute increase in Q and R, in the R more than in the Q and, therefore, a decrease in the Q/R ratio. The Q waves consistently increased in amplitude in both positions as auricular levels were approached. In each case, abnormal Q waves were obtained at one or more ventricular levels which were thought to be above the diaphragm.

In the 3 patients in whom the esophageal leads were taken in the sitting position only: the T waves were flat in one, upright in one, and inverted in one. In the 7 patients in whom records were taken in the erect and lying positions: the T waves were inverted in both positions in 4, upright in both positions in one, variable in both positions in one, and low to flat but somewhat variable in both positions in another. In general, assumption of the erect position caused the T wave to decrease in amplitude or become more deeply inverted. Records were made in one patient during deep inspiration and expiration. The Q waves were not changed in absolute size but were relatively increased in inspiration or expiration depending upon the effect of these on the size of the respective R waves.

DISCUSSION

White (21) stated that results of some interest had been obtained by exploring the base and posterior position of the left ventricle by means of the esophageal lead, but that the procedure was not clinically practicable. Levine (22) stated that QRS complexes in esophageal leads from ventricular levels should display prominent R waves and that, in cases of posterior myocardial infarction in which the standard leads are not diagnostic, esophageal leads may not only be warranted but are exceedingly valuable. Since the work of Hamilton and Nyboer (5), Nyboer (6–8), and Myers and Oren (9) have used the procedure more extensively in the diagnosis of posterior myocardial infarctions and have described cases in which an abnormal Q wave at the ventricular level was the only manifestation of previous infarction. Nyboer (7) considered a Q wave of over 4 mm. in the esophageal leads at the ventricular level to be indicative of a posterior myocardial infarction. Myers and Oren (9) suggested that a Q/R ratio of over 25 per cent in these leads may be a more valuable criterion. Helm, Helm, and Wolferth (23) studied esophageal patterns in 30 patients in a gastrointestinal clinic. They usually found Q waves of considerable magnitude between the auricular levels and the lower end of the esophagus but did not specifically state the size of these waves. They found the records from the lower end of the esophagus to be quite variable and to resemble the auricular pattern, the diaphragmatic pattern of Wolferth, Livesy, and Wood (24), or a combination of these. Occasionally they obtained bizarre records.

Although Helm, Helm, and Wolferth (23) usually found large Q waves just below the auricular level, Nyboer (6–8) and Myers and Oren (9) apparently did not often find them in patients who were believed not to have had posterior myocardial infarctions. Myers and Oren took esophageal leads on 44 of 50 subjects with prominent Q waves in lead III. Posterior myocardial infarctions were established in 21 patients by esophageal leads. In both of their cases of posterior myocardial infarction with a large Q3 but without Q $_{a}V_{f}$, esophageal leads suggested that the infarction was high on the posterior wall of the left ventricle

near the auricular margin. They excluded the possibility of myocardial infarction in 22 patients by negative esophageal leads.

In the present investigation it is believed that the position of the heart was a factor in the consistent production of the abnormal esophageal Q waves. In support of this belief are the variable findings in esophageal leads obtained by other authors, and the presence of abnormally large Q waves at ventricular levels, including levels above the diaphragm, in each of the 10 patients with pneumoperitoneum (4 with left phrenemphraxis and 3 with right phrenemphraxis). Moreover, differences in the size of the Q waves occurred when the position of the patient was altered or during various phases of respiration. The only consistent changes in the position of the heart in these patients was upward and forward displacement diagnosable by roentgenography. Upward displacement of the heart obviously would change the form of the esophageal electrocardiogram taken at specific distances from the nares. It is believed, however, that forward displacement, possibly with some forward rotation of the apex on the transverse axis, is the important factor in producing consistently large Q waves. It is not difficult to imagine the presence of an esophageal electrode at upper ventricular levels near the heart but far enough away so that the negative effect of the left ventricular cavity predominates. The presence of air between the electrode and various portions of the heart may have complicated the picture because the heart appeared to be displaced forward as well as upward in all cases and the diaphragm doubtless extended between the esophageal electrode and some portion of the heart in all. This did not appear to be the dominant factor in the production of large esophageal Q waves, however, because the Q waves increased in size as auricular levels were approached regardless of the height of the diaphragm and the relative levels of the right and left hemidiaphragms. In 5 of the 10 patients there were abnormally large Q waves at ventricular levels which were definitely above the diaphragm in the mid-line. In all 5, however, the diaphragm extended to higher levels laterally.

One patient (figure 3) was observed who had abnormally large Q waves in leads II, III, and $_{a}V_{f}$ and who showed low voltage in the standard and augmented unipolar limb leads. Myers and Oren (9) found that in 2 of 3 patients without infarction in whom Q $_{a}V_{f}$ was more than 25 per cent of R $_{a}V_{f}$ the QRS complexes were of low voltage, and stated that it was doubtful if much significance could be attached to large Q waves in $_{a}V_{f}$ when the voltage was small. Thus, it is doubtful that much significance could be attached to the abnormal Q waves in leads II, III, and $_{a}V_{f}$ noted in our patient, despite the fact that there were abnormally large Q waves in the esophageal leads at ventricular levels, because there were no Q waves before treatment and there were no symptoms suggestive of infarction after treatment and the T waves were not abnormal.

Benatt and Berg (11) stated that the electrocardiogram in pneumoperitoneum resembled the pattern of acute cor pulmonale and to a certain extent the Q_3T_3 pattern of myocardial infarction. Such electrocardiographic patterns did not appear in the present series.

Because of the tendency to use more and more chest leads clinically (25, 26)

and in research, the writers have developed a new system to facilitate description of locations of chest electrodes (20).

SUMMARY AND CONCLUSIONS

Ten patients, without suggestive evidence of heart disease, with pneumoperitoneum (4 with left and 3 with right phrenemphraxis) were studied with standard and augmented unipolar extremity electrocardiograms, numerous unipolar chest leads and esophageal leads, and with anteroposterior and lateral roentgenograms.

1. Pneumoperitoneum with or without phrenemphraxis affected the form of all leads to variable degrees but the changes were not always predictable.

2. Pneumoperitoneum may form abnormal Q waves in the standard or unipolar limb leads or the esophageal leads. Abnormally large Q waves, usually associated with abnormal T waves, were obtained in esophageal leads at ventricular levels in each of the 10 cases.

3. Interposition of air between the electrode and the heart did not appear to be the predominant factor in the production of the abnormally large esophageal Q waves because they were obtained above the level of the diaphragm and because the Q waves increased in size as auricular levels were approached, regardless of the height of the diaphragm or the relative heights of the right and left hemidiaphragms.

4. The position of the heart, especially forward displacement, was probably a factor in the production of the consistently abnormal esophageal Q waves because the heart was displaced upward and forward in each case.

5. Assumption of the upright position generally caused an increase in the amplitude of the esophageal Q and R waves, the R more than the Q, so that the Q/R ratio was decreased. The T waves decreased in amplitude or became more deeply inverted.

6. Deep respiration caused a slight change in the form of the esophageal electrocardiogram in the one case in which effects of respiration were studied.

7. The pattern of acute cor pulmonale and the large Q_3 with inverted T_3 pattern of myocardial infarction were not seen in this series.

SUMARIO

El Electrocardiograma en el Neumoperitoneo Comprendiendo Derivaciones, Unipolares Aumentadas de los Miembros

Diez enfermos, sin signos indicativos de cardiopatía, con neumoperitoneo (4 con frenenfraxis del lado izquierdo y 3 del derecho) fueron estudiados con electrocardiogramas unipolares corrientes y ampliados de los miembros, numerosas derivaciones unipolares torácicas y esofágicas, y con radiografías anteroposteriores y laterales.

1. El neumoperitoneo con y sin frenenfraxis afecta la forma de todas las derivaciones en grado variable, pero sin poderse predecir siempre las alteraciones.

2. El neumoperitoneo puede formar ondas Q anómalas en las derivaciones corrientes o unipolares de los miembros o en las esofágicas. En los 10 casos,

obtuviéronse, en las derivaciones esofágicas a los niveles ventriculares, ondas Q anormalmente grandes, por lo general asociadas a ondas T anómalas.

3. La interposición de aire entre el electrodo y el corazón no pareció ser el factor predominante en la producción de las ondas Q esofágicas anormalmente grandes, por haberse obtenido más arriba del nivel del diafragma y por aumentar en tamaño las ondas Q al acercarse a los niveles auriculares, independientemente de la elevación del diafragma o de las alturas relativas de los hemidiafragmas derecho e izquierdo.

4. La posición del corazón, y en particular el desplazamiento hacia adelante, fué probablemente un factor en la producción de las ondas Q esofágicas constantemente anormales, por hallarse en todos los casos el corazón desplazado hacia arriba y adelante.

5. La toma de la posición erecta ocasionó generalmente un aumento en la amplitud de las ondas esofágicas Q y R, las R más que las Q, de modo que disminuyó la razón Q/R. Las ondas T perdieron amplitud o se invirtieron más profundamente.

6. La respiración profunda motivó una leve alteración en la forma del electrocardiograma esofágico en el único caso en que se estudiaron los efectos de la respiración.

7. En esta serie no se observó el patrón del *cor pulmonale* agudo y la Q_3 grande con el patrón de la T_3 invertida del infarto miocardíaco.

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THE EFFECT OF PENICILLIN ON WOUND INFECTION AND OTHER COMPLICATIONS AFTER THORACOPLASTY[1]

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INTRODUCTION

The following is a report on the prophylactic use of penicillin given postoperatively following thoracoplasty stages performed at the New Haven Hospital in the two-year period from January 1, 1946 to January 1, 1948. The series comprises 104 operations, including 45 first-stage, 43 second-stage, and 16 third-stage thoracoplasties. There were no wound infections, in contrast to the statistics from most groups of cases done prior to the use of penicillin. The difference appears definite and important. Other postoperative complications encountered in this series are also presented.

The Problem

The importance of carrying out successive stages of a thoracoplastic procedure with a minimum delay between stages is recognized everywhere. Postoperative complications, though often quite minor in themselves, may cause undue delay in completion of the next stage. As minor a complication as a stitch abscess may sufficiently delay a following stage so as to preclude a maximal collapse effect, to say nothing of adding expense by prolonging the period of hospitalization. At the other extreme, when gross infection of thoracoplasty wounds has occurred, it has been associated with a high mortality.

Prior to the use of antimicrobial agents, the incidence of infection following general surgical operations was variously reported to be from 4 to 15 per cent (3, 6, 7). The incidence of infection in thoracoplasty wounds tended to be even higher (5, 7). As a consequence, various efforts have been made to decrease the incidence of infection. Such efforts have been concerned with decreasing contamination of the wound by special skin preparation, irradiation of operating rooms with ultraviolet light, use of silk instead of catgut, use of meticulous surgical technique, and finally the use of antimicrobial therapy. Some of the reported results of these efforts are listed in table 1.

In 1938 Hart (5) found that by the use of ultraviolet radiation in the operating rooms he was able to reduce the incidence of postthoracoplasty wound infection from a previous high of 33 per cent to 3.8 per cent. In 1940 Overholt and Betts (8) reported that by using the ultraviolet radiation along with a more meticulous operative technique, including the use of interrupted rather than continuous silk skin sutures and silver foil over the closed incision, they were able to reduce postthoracoplasty wound infection from 13.8 to 2.67 per cent. Moreover, most of the infections making up the 2.67 per cent were of a superficial nature.

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Other relevant points in technique have received emphasis elsewhere. The importance of using silk rather than catgut was demonstrated by Buxton and White (1), who compare a series of 538 thoracoplasties closed by the use of catgut with a series of 271 closed with silk. There were 18.9 per cent complications in the catgut series as compared with 7.0 per cent in the silk series.

In 1943 Cory (2) reported a reduction in thoracoplasty wound infection from 31 per cent to 1 per cent by the topical use of sulfathiazole. Similarly, Harrison and Berry (4), reporting a series of 107 cases of thoracoplasty at Bellevue Hospital during the period from 1938 to 1942, found an incidence of 2.3 per cent of operative wound infections. Sulfonamides had been used locally in the majority of their cases.

In 1943, Wu and Pianetto (9) reported a significant advance. Their procedure included elaborate precautions in skin preparation (the preparation of the skin

TABLE 1

Incidence of Postthoracoplasty Wound Infection as Reported in the Literature

YEAR	AUTHOR	STRESSED USE OF	INCIDENCE OF INFECTIONS
			per cent
1938	Hart (5)	Ultraviolet radiation in the operating room	3.8
1940	Overholt and Betts (8)	Ultraviolet radiation in operating room and interrupted silk skin sutures	2.7
1942	Harrison and Berry (4)	Local sulfonamides	2.3
1943	Cory (2)	Sulfathiazole locally	1
1943	Buxton and White (1)	Silk rather than catgut	7
1943	Wu and Pianetto (9)	Elaborate skin preparation	0
Present report		Penicillin postoperatively as a routine procedure	0

was begun several days preoperatively in each case) with particular care to keep the wound covered from air-borne contaminants during operation. They also attempted to use the least traumatic surgical technique, and used a minimal amount of suture material (catgut). With these practices they were able to report a series of 120 thoracoplasties in 55 patients without a single wound infection. Supplementary chemotherapy was not used.

A review of the wound complication data on thoracoplasties performed at the New Haven Hospital for the period from July 1934 to July 1940 (omitting the period from July 1936 to June 1937, during which year no data were recorded) has been made. During this period the wounds were scrutinized closely for signs of infection. Wounds were routinely inspected on the fifth postoperative day. Any particularly tight sutures were removed on this day. The remaining sutures were removed on the sixth and ninth days. The most superficial wound infections were recorded. A similar method of inspection was in use for the two-year period during which penicillin was used, so that we believe the figures are an

accurate reflection of the true conditions. During the "control" period from July 1934 to July 1940, out of a total of 59 stages there were three wound infections, an incidence of 5 per cent.

TECHNIQUE AND METHODS

The management of tuberculous patients for thoracoplasty at the New Haven Hospital is carried out according to the following general routine. After transfer to the hospital from a nearby sanatorium there is a two- or three-day period of observation during which time observations are made of temperature, pulse, and respiration; a blood count and urinalysis are done; throat cultures are made; a dental consultation is requested for prophylactic mouth care when this is indicated; and base-line examinations of the sputum or gastric contents for tubercle bacilli are made unless already available.

In the present series general anesthesia was used in most instances. More recently it has largely been supplanted by local anesthesia for the second and third stages of thoracoplasty.

For the first stage, the patients were usually intubated with an endotracheal tube, and cyclopropane was used in combination with various other agents. The most common combination was cyclopropane and ether following a pentothal induction (30 cases). In the 15 remaining first-stage operations, the anesthesia consisted of cyclopropane in various combinations with nitrous oxide, ether, ethylene, and avertin. In the second and third stages, similar combinations of the general anesthetic agents were used, but often with face-mask technique rather than endotracheal tube.

Operative technique does not include extensive preliminary skin preparation. The hemithorax is shaved the night preceding operation, and immediately before operation the skin is prepared by scrubbing with tincture of green soap, water, alcohol, and tincture of zephiran. No ultraviolet radiation has been used in the operating rooms. Interrupted fine silk technique is used throughout.

The incision used for the first stage is a hockey-stick type of incision beginning at the spinous process of the first dorsal vertebra, passing to within 1 to 2 cm. of the medial margin of the scapula at the level of the scapular spinous process. The incision then passes down along the medial margin of the scapula and curves forward around its inferior angle to the mid-axillary line. The trapezius is divided through its tendinous insertion to the scapula and split medially in the line of its muscle fibers, taking care to spare the accessory nerve. The rhomboid major is then divided along a line 1.0 cm. from the scapular vertebral margin and the upper anterior serratus divided to elevate the scapula. In the first-stage operation the upper three ribs are resected subperiosteally along with their transverse processes back to the vertebral laminae posteriorly. Anteriorly the first and second ribs are taken to or beyond their costocartilaginous junctions, the third to within a few centimeters of the costochondral juncture. Before resection of the first rib the scalene muscle attachments are divided extraperiosteally to prevent the tenting effect these muscles have on the regenerating first rib. Before closure of the wound is completed, the wound space between the collapsed muscle bundles and the overlying scapula is filled with normal saline and 100,000 units of aqueous penicillin. The saline serves to displace air pockets that may be confusing in postoperative roentgen evaluation of cavity closure and also serves to stabilize the chest wall somewhat in the immediate postoperative period before the fluid is completely absorbed. Closure of the wound is completed with interrupted silk technique to internal muscle layers, deep and superficial fascia, and skin. The incision is covered with silver foil and a dry gauze pressure dressing.

The second stage in cases for selective apical thoracoplasty has usually consisted of removal of appropriate lengths of the fourth, fifth, and sixth ribs, and sometimes a posterior section of the seventh. When removal of five or six ribs appears sufficient, resection of the lower third of the scapula is done to facilitate collapse and prevent riding of the scapula on the unresected ribs.

The third stage will usually require a second incision posterolaterally, and this is placed below and roughly parallel to the inferior part of the previous incision, taking care to leave a sufficiently wide margin of skin between the two so as not to embarrass circulation to the middle part.

The wounds are routinely inspected on the fifth postoperative day for any redness, tenderness, or other evidence of infection. Half of the skin sutures were usually removed on the sixth or seventh postoperative day and the rest on the ninth or tenth.

For all cases in the present series penicillin in aqueous solution was given intramuscularly every three hours to all patients for various lengths of time during the postoperative period. After the first-stage operation the average total dosage was 2,391,000 units over an average period of 9.0 days. The average total dosage after the second stage was 2,436,000 units for

TABLE 2

Postoperative Penicillin Dosage and Evidence of Infection

	FIRST STAGE	SECOND STAGE	THIRD STAGE
Number of cases	44	43	16
Average total penicillin	2,391,000 units	2,436,000 units	1,536,000 units
Average number of days on penicillin	9	9.4	6.7
Average highest temperature	101.3°	100.4°	99.6°
Average duration of fever in days	4.4	2.6	2
Local evidence of wound infection	0	0	0
Incidence of atelectasis:			
Ipsilateral	4	5	2
Contralateral	2	3	2
Pneumothorax	0	1	0
Pleural effusions	0	3	0
Spread of tuberculosis	2 (?3)	0	0

an average length of time of 9.4 days, while the corresponding figure for the third stage was 1,536,000 units over a 6.7-day period. More recently Duracillin has been made available and has supplanted aqueous penicillin. The Duracillin has been used in a dosage of 300,000 units twice a day and appears to be giving equally satisfactory results with the added convenience, for both patient and nurse, of fewer injections per day.

RESULTS

The highest oral temperature recorded during the preoperative week was noted in each case. The average highest temperature was 99.2° F. Penicillin was not given preoperatively except in 4 cases, where it was started on the day before operation. The total dosage of penicillin ranged from 30,000 to 240,000 units with an average of 165,000 units, and was administered in aqueous solution by the intramuscular route at three-hour intervals in all instances.

The significant postoperative data for all three stages have been summarized in table 2.

First-stage Thoracoplasties

In regard to the first-stage operations, the complications included one death. This occurred in a patient who was suffering from a mixed tuberculous empyema

and bronchopleural fistula, prostatic and epididymal tuberculosis, and pulmonary cavitary disease. He had a borderline ventilatory capacity, but his condition appeared to justify an attempt at collapse therapy. Death appeared to be due to a combination of respiratory insufficiency and chronic sepsis. In the remaining 44 cases, there were no wound infections of any kind. Atelectasis occurred in 6 cases, 4 on the ipsilateral side and 2 on the contralateral side. There was spread of the disease in at least 2 of these and probably in a third. There were no postoperative pneumothorax complications and no intrapleural effusions. Of the 6 instances of atelectasis, none were considered critical complications, most were minor, and further stages were carried out in each at regular intervals without delay. One drug reaction occurred and was manifested by urticaria and edema of the supraorbital regions and the extremities. It appeared on the thirteenth postoperative day, after 12 days of penicillin therapy, and disappeared after discontinuance of the penicillin.

The highest oral temperature recorded postoperatively was noted in each case. The average of these for the 45 cases was 101.4° F. Considering only those cases not complicated by spread of the tuberculosis, the average was found to be 101.3° F. The temperature elevation lasted no longer than three days in one-half of the patients, with an average of 4.4 days for the whole series.

Second-stage Thoracoplasties

There were 43 second-stage thoracoplasties with no deaths while the patients were in the hospital. The average peak oral temperature preoperatively was 98.9° F. In a sense the penicillin received by these patients after their first stage might be considered as preoperative preparation for the second stage. However, the length of time between the first and second stages varied in days from 12 to 23, with an average of 17, whereas the average course of penicillin after the first stage was only 9 days. In no instance was operation delayed because of the condition of the wound or skin. It is believed that the optimum interval between stages is 14 days and an attempt was made to adhere to this schedule in most cases. Some of the delays beyond the 14-day period were the result of crowded operating schedules. In the 6 cases which developed atelectasis after the first stage, the average interval between first and second stage was 17 days, i.e., identical with that of the entire series.

There were no complications in wound healing in the postoperative period. One wound was described as reddened on the seventh postoperative day and clear on the eighth. Atelectasis was noted in 8 cases, 5 on the ipsilateral side and 3 on the contralateral side. There was one pneumothorax. Pleural effusions were noted in 3 cases. These intrapleural and intrapulmonary complications occurred in 10 patients, of whom 2 had atelectasis of the same lobe following their preceding stage. All had cyclopropane and ether anesthesia, 9 with pentothal and one with nitrous oxide induction. None of the group was seriously ill. The temperature returned to normal on the second postoperative day in 4; on the third, in 3; and on the fourth, sixth, and eighth postoperative day in the others.

There were no recognized instances of further spread of the tuberculosis in

this series, and no evidence of drug reaction was noted. The average highest postoperative oral temperature rise for the second stage was appreciably lower than that of the first stage, being 100.4° F. The elevation lasted no longer than two days in more than one-half of the patients (26), with an average of 2.6 days.

Third-stage Thoracoplasties

Sixteen cases received a third-stage procedure. Among these the average highest preoperative temperature was 98.7° F. The interval between second- and third-stage procedures ranged from 14 to 31 days, with a 19.7 average. There was no delay for wound or pulmonary complications in this group. The longer span between second and third stages represents in some cases a period of indecision when the necessity for a third stage was being debated. It is not believed that the same urgency for speed obtains once the scapula has been dropped inside the costal cage level.

There were no complications of wound-healing during the postoperative period. Atelectasis was noted in 4 cases, 2 ipsilateral and 2 contralateral, and in no case was it of more than minor consequence. The highest postoperative oral temperature in these 4 instances was 100.8° F., 99.4° F., 100.4° F., and 100.2° F., respectively. The temperature had returned to normal within four days in all 4 patients. There were no intrapleural complications, no evidence of further spread of the tuberculosis, and no evidence of drug reactions.

The average highest postoperative oral temperature was 99.6° F. Again in more than one-half of the cases the temperature had returned to normal after the second postoperative day and the average febrile period was only 2.0 days.

SUMMARY

A series of 104 thoracoplasty stages performed on 45 patients has been presented. One death occurred on the second postoperative day and was thought to be consequent to a combination of respiratory insufficiency and chronic sepsis. During the remaining 103 thoracoplasty stages the patients all received postoperative parenteral penicillin therapy. There were no complications in wound-healing. The time between stages was not delayed in any case because of wound infection. Presumptive evidence of a hypersensitivity reaction to penicillin was observed in only one patient. Because of the observations in these cases, as contrasted with a "control" group from the same service as well as the results reported in the literature prior to the use of penicillin, it is believed that the routine use of intramuscular penicillin postoperatively in all thoracoplasty stages is justified.

SUMARIO

El Efecto de la Penicilina sobre las Heridas Infectadas y Otras Complicaciones Consecutivas a la Toracoplastia

La serie descrita comprende 104 tiempos de toracoplastia ejectuados en 45 enfermos. Una muerte en el segundo día postoperatorio pareció debida a una combinación de insuficiencia respiratoria y septicemia crónica. En los otros 103

tiempos toracoplásticos se administró penicilina por vía parentérica postoperatoriamente. No hubo complicaciones en lo tocante a cicatrización de las heridas. En ningún caso se retardó el tiempo transcurrido entre etapas operatorias debido a infección de las heridas. Sólo en un paciente se observaron signos presuntivos de reacción de sensibilidad a la penicilina. Por virtud de lo observado en esos casos, comparados con un grupo de testigos de los AA. así como con otros comunicados en la literatura antes de emplearse la penicilina, parece justificado continuar el empleo sistemático de la penicilina por vía intramuscular postoperatoriamente en todos los tiempos de la toracoplastia.

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APPENDICITIS DURING PNEUMOPERITONEUM TREATMENT[1,2]

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The relationship of appendicitis to pneumoperitoneum is disputed. It has been stated that appendicitis occurs eleven times more frequently in patients receiving pneumoperitoneum therapy than in the remainder of the sanatorium population (1). On the other hand, some authors do not even list appendicitis as a complication of pneumoperitoneum treatment (2). Mitchell and his co-workers (3) found but one instance of appendicitis in 710 patients receiving pneumoperitoneum.

All the patients treated at the Oteen Veterans Administration Hospital between January 1947 and May 1949 were selected for study because all of the appendices removed during that period were personally examined by the author. Sections were also stained for acid-fast bacilli whenever a histologic diagnosis of tuberculosis was made. Table 1 presents the pertinent data. This shows that patients receiving pneumoperitoneum developed appendicitis five times more frequently than the remainder of the hospital population. In three-fourths of the pneumoperitoneum group the appendix was acutely inflamed. Some also had tuberculosis of the appendix.

The effects of air in the abdominal cavity on the peritoneum and the appendix were investigated by histologic methods. Some of the patients receiving pneumoperitoneum were operated on for various abdominal conditions. None of this group had any disease that would cause peritonitis. During the operation, portions of peritoneum were removed from the anterior abdominal wall. Study of this material occasionally revealed thickening of the mesothelial layer. The infrequent occurrence of a nonspecific inflammatory reaction in the peritoneum has been reported by other investigators (4, 5). The mesothelial thickening indicates peritoneal irritation and it is possible that such irritation may initiate the changes that produce appendicitis. It was impossible to tell which patients were receiving pneumoperitoneum from the histologic examination of the appendices. The cases of acute appendicitis in both the treated and untreated groups showed similar involvement of the various appendicular layers.

Three of the tuberculous appendices in the pneumoperitoneum group also showed nonspecific inflammatory changes and their removal was indicated. The remaining tuberculous appendices were apparently removed because of the difficulty of differentiating acute appendicitis from tuberculosis of the ileocecal region in the presence of abdominal air. Certainly there must have been some individuals with ileocecal tuberculosis in both groups of patients. It may be

[1] From the Department of Pathology, Veterans Administration Hospital, Oteen, North Carolina.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

that intestinal tuberculosis is more easily diagnosed in the nontreated group and is therefore not operated on as "appendicitis." The signs and symptoms of appendicitis in the presence of pneumoperitoneum are occasionally bizarre. Because of the difficulty of differential diagnosis in the presence of pneumoperitoneum, there is sometimes a tendency to delay the operation until the diagnosis of appendicitis is more reasonably certain. This delay may account for the more advanced inflammatory changes in the removed specimens. A large part of the appendices removed from the remainder of the hospital population showed fibrosis or minimal inflammatory changes.

TABLE 1

Incidence of Appendicitis

	WITH PNEUMOPERITONEUM	WITHOUT PNEUMOPERITONEUM
Number of patients	981	3,240
Total number of appendectomies	16 (1.63 per cent)	12 (0.37 per cent)
Appendices showing acute inflammation	11 (1.12 per cent)	6 (0.19 per cent)
Without tuberculosis	8	6
With tuberculosis	3	0
Total appendices with tuberculosis	5	0

Although acute appendicitis occurred more frequently in patients receiving pneumoperitoneum than in the remainder of the hospital population treated for pulmonary tuberculosis, the incidence is still small enough to be of no great clinical significance. Certainly the benefits derived from pneumoperitoneum in the treatment of pulmonary tuberculosis far outweigh the dangers from a slightly increased occurrence of appendicitis.

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BRONCHOSCOPY IN A SANATORIUM[1,2]

A Review of 522 Consecutive Bronchoscopies

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INTRODUCTION

A review has been made of some of the findings in a series of 522 consecutive bronchoscopies at the Nova Scotia Sanatorium. These examinations were not part of a routine investigation. Each case was selected by the medical staff because of definite symptoms, signs, or roentgenographic evidence of tracheobronchial disease, or in order to elicit additional information such as source of hemoptysis or tubercle bacilli in sputum. The patients were bronchoscoped, especially in the early part of the series, with a certain skepticism as to the value of this procedure in the treatment of tuberculous tracheobronchitis. At that time a diagnosis of this condition was not made unless there was definite ulceration which could be demonstrated. Later in the series it was believed that the presence of localized edematous reddened membrane around the orifice of an involved lobe should be considered as indicative of a tuberculous tracheobronchitis, which should be classified as type I.

All of the patients were examined under local anesthesia. They were given a routine preoperative medication of 0.1 Gm. of phenobarbital and 0.010 to 0.015 Gm. of morphine with 0.0004 Gm. of atropine at two-hour and one-hour intervals, respectively, before administration of the local anesthetic. The latter consisted of two applications of 2 per cent pontocaine to the pyriform sinuses and the instillation of 1.5 to 2.0 cc. of 2 per cent pontocaine into the trachea. Atropine was omitted in cases where specimens of secretion were to be collected for examination. Twelve patients were usually examined at one session which averaged about three hours. All the bronchoscopies were done by one of the writers (D. MacR.), while another (J. J. Q.) administered practically all the anesthesia; all of the charts and roentgenographic findings were reviewed by the other member (J. E. H.)

OBSERVATIONS

Three hundred eight-three patients were examined in the series. Of this number, 335 were patients with tuberculosis upon whom 476 bronchoscopies were performed, while 45 of the patients were considered to be nontuberculous (table 1). Most of the latter had been admitted to the sanatorium merely for investigation.

Nontuberculous patients: In the group without evidence of tuberculosis (table 2) were 12 cases of bronchiectasis, 4 cases of lung abscess, 5 cases of carcinoma,

[1] From the Nova Scotia Sanatorium, Kentville, Nova Scotia, Canada.

[2] Presented at the annual meeting, Canadian Tuberculosis Association, Halifax, June 24, 1949.

3 cases of cardiac disease, 2 cases of aneurysm, and 2 cases of lymphosarcoma, as well as a few other miscellaneous conditions. There was only one febrile reaction of more than one degree Fahrenheit, and there were no anesthetic reactions or other complications associated with the bronchoscopic examinations in this group.

Three of these patients were not bronchoscoped because laryngeal examination showed the presence of a small ulcerative tuberculous laryngitis which had not previously been suspected.

TABLE 1

525 Bronchoscopies—An Analysis of Conditions Found

DIAGNOSIS	CASES	EXAMINATIONS
Tuberculous	335	476
Nontuberculous	45	46
Tuberculous laryngitis—laryngoscopy only	3	3
Total	383	525

TABLE 2

Nontuberculous Conditions—Diagnoses

DIAGNOSIS	NUMBER OF PATIENTS	DIAGNOSIS	NUMBER OF PATIENTS
Abscess of lung	4	Infarction	1
Aneurysm	2	Lipoid pneumonia	1
Asthma	1	Lymphosarcoma	2
Bronchiectasis*	12	Pleurisy with effusion	1
Carcinoma	5	Postoperative resection*	1
Cardiac disease	3	Pulmonary fibrosis	1
Congenital abnormality	1	Sarcoid	1
Cyst-bronchial	1	Undiagnosed	2
Hilar adenopathy—benign	2	No disease	5
Total			46

* One case examined twice with different diagnoses.

Tuberculous patients: Sixty-two cases of tuberculous tracheobronchial disease were found in the group of 335 patients with pulmonary disease (table 3). These were classified as follows under four of the five types described by Judd (1):

Type I—The lesions consist of superficial inflammatory reaction and may be progressing to show a superficial ulceration. Seventeen cases were in this group.

Type II—Definite ulceration of variable size and number is present with some surrounding inflammatory reaction and even granulation overgrowth. Thirty-four cases were in this group.

Type III—More extensive ulceration is present than in type II and there is fixation of surrounding tissue and masses of granulation tissue or even actual stenosis. Five cases were in this group.

Type IV—The ulceration has healed and the inflammatory reaction has subsided but actual stenosis is present. These are considered as healed lesions. Six cases were in this group.

Most of the lesions were on the posterolateral walls and were unilateral. In several cases a main bronchus was almost completely occluded. Three of the lesions involved the trachea only, eight were present in both trachea and a main bronchus, while fifty-one were seen in the bronchi only.

TABLE 3

Tuberculous Cases—Diagnoses

BRONCHOSCOPIC FINDINGS	NUMBER	PER CENT
Tuberculous tracheobronchitis	62	18.5
Type I 17		
Type II 34		
Type III 5		
Type IV 6		
Normal findings	273	81.5
Total	335	100.0

TABLE 4

Tuberculous Cases—Age and Sex Distribution

AGE GROUP	TRACHEOBRONCHITIS		NO TRACHEOBRONCHITIS		TOTAL	
	Male	Female	Male	Female	Male	Female
10 to 19	1	7	4	7	5	14
20 to 29	3	24	47	67	50	91
30 to 39	2	16	46	40	48	56
40 to 49	5	3	25	13	30	16
50 to 59	0	1	16	1	16	2
60 to 69	0	0	5	1	5	1
70 to 79	0	0	0	1	0	1
All ages	11, or 7%	51, or 28%	143, or 93%	130, or 72%	154	181
Total	62, or 18.5%		273, or 81.5%		335, or 100%	

Age and sex distribution: There were 181 females, or 54 per cent of the group, compared with 154 males, or 46 per cent, and age of the patients varied from 11 to 73 years (table 4). Tracheobronchial disease was found in only 7 per cent of the males as compared with 28 per cent of the females who were bronchoscoped. This is a ratio of 1:4, showing in this series a marked tendency of the female patients to develop this complication.

Extent of pulmonary disease: The frequency of tracheobronchitis increased with the extent of the pulmonary disease (table 5). It was found in 11 per cent of the 27 patients with minimal disease, in 17 per cent of the 193 patients with

moderately advanced disease, and in 23 per cent of the 113 patients with far advanced disease. The same tendency pertained even in the presence of collapse measures. It is interesting to note that 100 patients with thoracoplasty were bronchoscoped and 19 were found to have tracheobronchitis. These 100 patients represent approximately 11 per cent of the patients who have had thoracoplasties at the Nova Scotia Sanatorium. This does not mean that in all 11 per cent the results were ultimately unsatisfactory, for some of them, bronchoscoped early during their convalescence, went on to good recovery and the majority of those with tracheobronchitis responded to specific treatment.

Incidence of tracheobronchitis: There is quite a variation in the frequency of tracheobronchitis as reported in the literature. McIndoe (2) reports finding 11

TABLE 5

Tuberculous Cases—Extent of Pulmonary Disease

EXTENT OF DISEASE	TRACHEO-BRONCHITIS		NO TRACHEO-BRONCHITIS		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Minimal	3	11	24	89	27	100
Moderately advanced	33	17	160	83	193	100
Far advanced	26	23	87	77	113	100
Pleurisy with effusion	0	0	1		1	
Tuberculous empyema	0	0	1		1	
Total	62		273		335	
M. A. with thoracoplasty	5	10	46	90	51	100
F. A. with thoracoplasty	14	28	35	72	49	100
Total with thoracoplasty	19		81		100	
Min. with artificial pneumothorax	0		1		1	
M. A. with artificial pneumothorax	5	15	28	85	33	100
F. A. with artificial pneumothorax	4	31	9	69	13	100
Total with artificial pneumothorax	9		38		47	

per cent in patients bronchoscoped routinely on admission. Warren (3) found 13 per cent in a series of 90 patients examined before thoracoplasty and 57 per cent in 108 patients examined because of symptoms. Judd (1) found 36.8 per cent in a study of 500 consecutive cases of tuberculosis. The variation is equally as great in the reported incidence from autopsy findings of patients who died of tuberculosis. Flance and Wheeler (4) found tracheobronchitis in 3.1 per cent of 285 autopsies and Auerbach (5) reported it in 4.4 per cent of 316 autopsies, while Bugher (6) found tuberculous lesions of the trachea and main bronchi or both in 41 per cent of 122 autopsies, and Salkin (7) reported an incidence of 40 per cent in 125 autopsies.

Atelectasis: Atelectasis (table 6) was present in 99 of the patients or in 30 per cent of the group. Fifty-five per cent of the cases of tracheobronchitis showed evidence of atelectasis while it occurred in only 24 per cent of the non-tracheobronchitic group. Salkin (7), in a review of 622 patients bronchoscoped, found

atelectasis in 36 per cent of patients with tracheobronchitis and in 12 per cent of a group of patients without tracheobronchitis.

Segmental atelectasis was found in 48 patients in the series of 335 cases, but 23 or 48 per cent of these were found in the 47 patients with pneumothorax.

TABLE 6

Tuberculous Cases—Incidence of Atelectasis

ATELECTASIS	TRACHEO-BRONCHITIS	NO TRACHEO-BRONCHITIS	TOTAL
Segmental	9	16	25
Segmental (Px.† present)	2	21	23
Segmental (Thor. present)	0	0	0
Lobar	9	11	20
Lobar (Px. present)	3	4	7
Lobar (Thor. present)	4	5	9
Massive	1	2	3
Massive (Px. present)	1	1	2
Massive (Thor. present)	5	5	10
All types	34, or 55%	65, or 24%	99, or 30%
Not known	1	3	4
None	27	205	232
Total	62	273	335

* Thoracoplasty

† Artificial Pneumothorax

TABLE 7

Tuberculous Cases—Atelectasis—Sex Incidence

ATELECTASIS	TRACHEO-BRONCHITIS		NO TRACHEO-BRONCHITIS		TOTAL	
	Male	Female	Male	Female	Male	Female
Segmental	0	11	17	20	17	31
Lobar	3	13	11	9	14	22
Massive	1	6	4	4	5	10
Not stated	0	1	2	1	2	2
None	7	20	109	96	116	116
Total	11	51	143	130	154	181
Per cent with atelectasis	36	60	23	26	23	35

This may be accounted for in part by obstruction caused by a reduction of the bronchial lumen or actual mechanical kinking of a bronchus. It is more reasonable, however, to consider the segmental atelectasis as being primarily a result of the presence of tuberculous tracheobronchitis in the smaller bronchi beyond the bronchoscopic field of vision.

Atelectasis (table 7) was twice as common in the female patients with tracheobronchitis as it was in the males. In the patients without tracheobronchitis,

the occurrence was about equal in the two sexes. It would seem that there is a tendency for females to show areas of atelectasis, which may be associated with the greater preponderance of tuberculous tracheobronchitis in this sex. It follows therefore, that atelectasis is suggestive of the presence of tuberculous tracheobronchitis, especially when it is found in the female.

Presence of rhonchi: Rhonchi (table 8) were found in 40 per cent of the cases with tracheobronchial disease but in only 17 per cent of the other patients. In the cases of tracheobronchitis, rhonchi were found in 43 per cent of the females and 27 per cent of the males, while in the cases without tracheobronchitis rhonchi were reported in 19 per cent of the males and in 16 per cent of the females. These are similar ratios to those observed in regard to atelectasis. Thus, it is evident that rhonchi may indicate the presence of tuberculous tracheobronchitis, although they may also be caused by excessive secretion in the bronchi from other causes.

TABLE 8

Tuberculous Cases—Incidence of Rhonchi

RHONCHI	TRACHEO-BRONCHITIS		NO TRACHEO-BRONCHITIS		TOTAL	
	Male	Female	Male	Female	Male	Female
Present	3	21	27	20	30	41
Not stated	0	2	3	4	3	6
None	8	28	113	106	121	134
Total	11	51	143	130	154	181
Per cent with rhonchi	27	43	19	16	20	23

Reaction to anesthesia: There were 8 reactions to anesthesia in the series. Five reactions, or 3 per cent, occurred in the 172 bronchoscopies in tracheobronchitis patients, while 3 reactions, or one per cent, occurred in the 304 bronchoscopies on patients without tracheobronchitis. The reactions were of moderate degree in 4 patients and severe in the others.

Three of the reactions to anesthesia occurred on the first bronchoscopic examination, 2 on the second, one on the third, and 2 on the fourth. The reactions were of two types. In one, the patient became semicomatose with a mild clonic type of spasm which passed off after an intravenous injection of 0.3 Gm. of sodium phenobarbital. In the other type the symptoms were more alarming and characterized by dyspnea, cyanosis, and marked wheezing. These patients were treated with various doses of epinephrine and bronchoscopic aspiration of secretions with the administration of oxygen through the aspirating tube of the bronchoscope. A considerable amount of frothy watery secretion was usually found in the trachea and main bronchi, but wheezing still continued after all visible secretions had been removed.

Bacteriologic studies: Sputum examinations by smear, concentration, or culture

were positive for tubercle bacilli in 88 per cent of the cases of tracheobronchial disease and in 73 per cent of the patients without tracheobronchitis.

An analysis (table 9) of specimens of secretion taken during the bronchoscopic examination shows that an appreciable number were found positive for the tubercle bacillus. Routine collections of secretion were not made, but were taken for special purposes in 109 cases. In one case of tracheobronchitis, the secretions were positive by smear but negative for *M. tuberculosis* on culture. This finding suggested the possibility that the bacilli seen in the smear represented a con-

TABLE 9

Tuberculous Cases—Results of Examination of Secretion Obtained at Bronchoscopy

	TRACHEOBRONCHITIS	NO TRACHEOBRONCHITIS	TOTAL
Not examined	162	205	367
Negative for tubercle bacilli			
Smear	1	4	5
Concentration	0	0	0
Culture	5	50	55
Positive for tubercle bacilli			
Smear	1	1	2
Concentration	0	0	0
Culture	1	17	18
Smear *Pos.* Culture *Neg*	1 (Sputum+)	11 (Sputum +=8, Sputum 0=3)	12
Smear *Pos.* Culture *Neg*	1	16	17
Total	172	304	476
Br. Sec.* 0 Sputum +	5	32	37
Br. Sec. + Sputum +	4	41	45
Br. Sec. 0 Sputum 0	1	22	23
Br. Sec. + Sputum 0	0	4	4
Totals	10	99	109

* Bronchoscopic secretions.

taminant present in the sterilized aspirating tube. On another occasion, however, tubercle bacilli were present in a culture of sputum from this patient.

In 11 cases without tracheobronchitis, the smear of the sputum was positive for acid-fast bacilli, but culture of the bronchoscopic specimen was negative. Eight of these patients had sputum positive for tubercle bacilli, but it is possible that some of the organisms seen on direct smear were dead contaminants, as they did not grow on culture.

Only 4 patients were found to have a positive sputum by means of examination of the bronchoscopic specimen when the routine sputum tests had been negative for acid-fast bacilli. On the other hand, of 37 patients with a known positive sputum, the bronchoscopic specimens were negative for tubercle bacilli. In the other 68 cases the findings of the two methods of examination were in agreement.

It appears that repeated routine sputum tests by concentration and culture methods are more efficient in obtaining positive results than examination of bronchoscopic specimens, but in 4 instances a diagnosis was made only as a result of obtaining secretions by bronchoscopy.

Treatment: In the earlier cases of tracheobronchitis, the treatment consisted of repeated bronchoscopic applications of 30 per cent silver nitrate. Twenty-two patients were so treated, with clearing of the visible disease in 76 per cent (table 10). Eighteen patients were treated with streptomycin. In the earlier cases streptomycin aerosol, 0.5 Gm. a day, was given for two weeks, plus 0.5 Gm. of streptomycin intramuscularly twice a day for at least two months. During the

TABLE 10

Tracheobronchitis Treatment

	STREPTOMYCIN					SILVER NITRATE				BOTH		NO THERAPY
	NUMBER	Under 1 month	One to two months	Two to three months	Over 3 months	NUMBER	Under 1 month	One to two months	Two to three months	Over 3 months	Number	Over 3 months	Number
Lesion disappeared	15	1	6	6	2	16	3	0	3	10	2	2	1
Lesion improved	2					2							0
Lesion stationary	0					0							1
Lesion worse	1					3							1
Lesion stenosed	0					0							5
Not stated						1							13
Total	18					22					2		21

N. B. One relapse from silver nitrate later treated with streptomycin (tabulated as two cases).

past year the intramuscular treatment only was used. Eighty-three per cent of these patients showed a good response by apparent clearing of the tracheobronchitis. Two patients were treated with both silver nitrate and streptomycin with good results. The patients treated with streptomycin showed good results in a much shorter period of time. For example, with streptomycin, apparent complete clearing occurred in 47 per cent of cases in less than two months, while with silver nitrate it occurred in only 18 per cent. Moreover, in less than three months streptomycin gave 87 per cent apparent clearing compared with 37 per cent with silver nitrate.

Five patients with bronchial stenosis were not treated, as it was felt that dilatation of stenosed bronchi did not result in any appreciable improvement. It is believed that resection, if feasible, is the treatment of choice in these cases.

Thirteen patients with tracheobronchitis diagnosed early in the series were not treated by either method. In a number of these patients, thoracoplasty opera-

tions were carried out as specific treatment for the tracheobronchitis. The clinical results appeared to be satisfactory although the patients were not bronchoscoped subsequently.

In brief, then, it seems that streptomycin gave a better result than silver nitrate, and produced it more quickly. Moreover, streptomycin presumably had a favorable result on bronchial lesions beyond the vision of the bronchoscopist where silver nitrate could not be applied because of inaccessibility. Silver nitrate, however, was of definite value at a time when streptomycin was not available.

Febrile reactions: The bronchoscopic examinations were followed by a febrile reaction of over one degree Fahrenheit in 9 per cent of the procedures (table 11). Twelve per cent of the examinations upon tracheobronchitics were followed by such a reaction while 6 per cent of the group without tracheobronchitis and only

TABLE 11

Tuberculous Cases—Incidence of Febrile Reactions

DEGREE	TRACHEOBRONCHITIS		NO TRACHEOBRONCHITIS	TOTAL
	First examination only	All examinations		
None	26	86	216	302
Under 1° F.	19	51	42	93
1° to 2° F.	3	8	9	17
2° to 3° F.	6 (21 per cent)	4 (12 per cent)	3 (6 per cent)	7 (9 per cent)
Over 3° F.	3	7	6	13
Not stated	5	16	28	44
Total	62	172	304	476

2 per cent of the nontuberculous patients had such an elevation of temperature. It is significant to note that, if the patients with tuberculous tracheobronchitis were considered from the point of view of their first examination only, or before any treatment of the tracheobronchial lesion was given, significant febrile reactions occurred in 21 per cent.

Postbronchoscopic spread of tuberculosis: In attempting to evaluate any adverse effects that may be associated with the bronchoscopic procedure, it is impossible to assess properly the factor of postbronchoscopic roentgenographic evidence of extension of the pulmonary disease. In reviewing the literature, it was found that McIndoe (2) reported a series of 272 tuberculous patients bronchoscoped, with only 4 showing an extension of disease shortly after bronchoscopy. Hawkins (8) found a spread of disease in only one case, but had 3 deaths in 516 bronchoscopies. Warren (3) reported 2 cases of spread of disease and Jenks (9) also reported 2 such cases. Several authors reported the occurrence of single instances of spread of disease in their series. Most of the papers on bronchoscopy in pulmonary tuberculosis did not deal with or report on this complication directly but stated that there were no spreads of disease that could be attributed to the

procedure. However, Radner (10), reporting on 183 bronchoscopic examinations on 97 patients with pulmonary tuberculosis, found that 21 procedures were followed by a minimal infiltrative spread, and 5 were followed by atelectasis. The most comprehensive review of this aspect of bronchoscopy was by Coates (11). In 1948 he reported a study of postbronchoscopic increase of pulmonary tuberculosis in a series of 473 bronchoscopies on 233 patients at Trudeau Sanatorium from October 1936 to October 1946. He found that 73 bronchoscopies were followed by a roentgenographic increase within two months, an incidence of 15 per cent "spread" which occurred about equally in the tracheobronchitis and the non-tracheobronchitis patients. There had been routine chest roentgenograms at two-month intervals for at least six months before and six months after

TABLE 12

Tuberculous Cases—Extension of Disease before and after Bronchoscopy

BEFORE* BRONCHOSCOPY	AFTER* BRONCHOSCOPY	TRACHEOBRONCHITIS		NO TRACHEOBRONCHITIS	
		Actual	Expected	Actual	Expected
No extension	No extension	33	28 per cent extended	189	6 per cent extended
No extension	Extension	13		12	
Extension	No further extension	5	61 per cent extended	30	22 per cent
Extension	Further extension	8		7	
Not stated		3		35	
Totals		62 (35 per cent extended)		273 (8 per cent extended)	

* Within approximately three months.

bronchoscopy. His conclusion after reviewing the series of films was that the roentgenographic increase of disease in the two months immediately following bronchoscopy was no greater than in other two-month periods before bronchoscopy.

In this series, roentgenographic evidence of spread of disease was found to have occurred after 12 per cent of the bronchoscopies. It should be noted, however, that spread of disease occurred in 35 per cent of the tracheobronchitic group compared with an incidence of only 8 per cent in the patients with no tracheobronchitis (table 12).

It is realized that the value of statistics in such a small series is questionable. Nevertheless, it is desirable to try to distinguish between postbronchoscopic "spreads" and "spreads" which might have occurred without this procedure. Fifty-nine of the patients with tracheobronchitis had roentgenograms within a three-month period before and after bronchoscopy (table 12). In 22 per cent of these patients, roentgenographic evidence of extension of disease was demon-

strable before the examination. Thus, it may be concluded that the extensions which might be expected after bronchoscopy would be approximately the same. By the same reasoning, the expected rate of extensions in the group without tracheobronchitis was 16 per cent. In the tracheobronchitis group spreads of disease occurred in 28 per cent of those who had not had previous "spreads," which was only slightly in excess of the expected rate. In patients showing extension prior to bronchoscopy, 61 per cent had further extension after the procedure. This value is almost three times the expected rate for this group as a whole, although further extensions might well follow unstable disease showing previous extension rather more frequently than where no previous extension had occurred. Of the patients with no tracheobronchitis, only 6 per cent of those with no prior extension showed "spread" after the bronchoscopy. This was much less than the expected 16 per cent occurrence of spread, but this group contained most of the 81 patients with thoracoplasty who were investigated because of sputum positive for tubercle bacilli. These cases, already compressed, would not

TABLE 13

Cases of Tracheobronchitis—Extensions under Streptomycin Treatment

RESULT UNDER TREATMENT	CASES
No extension of lung lesion	15
Extension of lung lesion	3, or 17%
Tracheobronchial disease cleared	15
Tracheobronchial disease improved	2
Tracheobronchial disease worse	1, or 7%

be expected to contribute many extensions following such a procedure. Thus, the expected and actual rates of extension in this group might be considered as reasonably comparable. It would appear that, while bronchoscopy is a relatively harmless procedure in patients without tracheobronchitis, it has a definite tendency to cause exacerbations of disease in the presence of tuberculous tracheobronchitis.

Streptomycin is a valuable drug but it was not completely effective in staying the progress of tuberculous tracheobronchitis nor of its concomitant pulmonary disease (table 13). The effect of the drug on the former was better than on the latter, and in both conditions it was shown to be extremely valuable.

Deaths: Three deaths occurred in the entire series of 383 patients.

CASE REPORTS

Case 1. The patient was a female 29 years of age who had been receiving treatment for tuberculosis at irregular intervals for the previous nine years. She had had an artificial pneumothorax on the left side which had been discontinued five years previously, and one on the right side which had been discontinued four years previously. She was readmitted to the Nova Scotia Sanatorium because of severe bronchitic symptoms with fever and sputum positive for tubercle bacilli during the past four months. Roentgenographic examination showed a recent atelectasis of the right upper lobe. On bronchoscopy there was a consider-

able amount of mucopurulent secretion in the trachea and right main bronchus. The right upper lobe orifice was obstructed by thick gelatinous exudate and granulation tissue. The curved flexible aspirator was introduced and, after considerable suction, there was apparently some aeration of the lobe as secretion present in the bronchus could be seen moving to and fro during respiration. The ulcerations were treated with 30 per cent silver nitrate. That afternoon she experienced chills and fever up to 103° F. The following day a roentgenogram showed apparent ventilation of the right upper lobe and the presence of a large cavity. She continued to run an afternoon temperature of 101° F. with increasing cough expectoration, and recurring chills. She died on the fourteenth day, having required oxygen at intervals during the preceding few days because of dyspnea and cyanosis.

Case 2. The patient was a female 31 years old who had received treatment for tuberculosis over a period of eight years. Two years previously she had had a thoracoplasty performed on her right side, at which time a bronchoscopic examination had shown ulceration and stenosis of the right main bronchus. A second bronchoscopy was requested prior to consideration of further compression therapy. On administration of the local anesthetic, the patient became semicomatose with marked dyspnea and cyanosis. The bronchoscope was inserted and frothy secretion was aspirated from the trachea and both main bronchi. Oxygen was administered through the aspirating channel in the bronchoscope until the cough reflex returned and the patient was able to sit up with assistance. She continued to have dyspnea, and a roentgenogram showed new infiltrative changes in the upper lobe and bronchopneumonic changes in the lower part of the left lung field. Dyspnea and cyanosis persisted and the patient died on the thirtieth day after the procedure.

Case 3. The patient was a female 34 years of age. She had entered the sanatorium four years before with a bilateral pulmonary tuberculosis, tuberculous laryngitis, tuberculous colitis, and tuberculous glossitis. She gradually improved enough to permit the first stage of a thoracoplasty on the left side in October 1944. In April 1945 she was bronchoscoped because of severe asthmatic attack which had prevented further surgery. The bronchoscopic examination revealed a definite stenosis of the left main bronchus but no ulceration. She was bronchoscoped a second time on June 2 and a third bronchoscopy was done on July 11. This revealed an ulcerative tuberculous tracheobronchitis at the junction of the trachea and right main bronchus. The stenosis of the left main bronchus was not quite so marked as on the previous examination. During the following two weeks the patient was critically ill with dyspnea and cyanosis. On September 2 she still had marked wheezing but, in spite of this, it was felt that she was doing so poorly that another bronchoscopic examination should be done. Following administration of local anesthesia, the patient developed a marked reaction with cyanosis, dyspnea, and semiconsciousness. The bronchoscope was used only for aspiration of frothy secretion and administration of oxygen, with no further instrumentation being performed. Although the severity of the reaction subsided in fifteen to twenty minutes, the patient had considerable dyspnea and cyanosis, and died the following day.

After reviewing these 3 cases, it was felt that 2 of the cases were unsuitable for bronchoscopy, and the deaths of cases 2 and 3 were probably due to anesthetic reactions. If similar cases were selected for bronchoscopic examination today, they would be done under laryngeal anesthesia only. Several patients who had had a reaction to the instillation of pontocaine were bronchoscoped a number of subsequent times without instilling any anesthesia into the trachea. These bronchoscopies were performed without difficulty or apparent reaction.

SUMMARY

1. An analysis of 522 bronchoscopic procedures has been presented.

2. Tuberculous tracheobronchitis was found four times as commonly in females as in males in a series of 335 patients with pulmonary tuberculosis.

3. Atelectasis and rhonchi were twice as common in females as in males and presumably were related to the presence of tuberculous tracheobronchitis.

4. Acid-fast bacilli found by examination of secretions removed bronchoscopically should not be considered confirmatory evidence of pulmonary tuberculosis unless cultures of the material yield tubercle bacilli.

5. The incidence of appreciable febrile reactions following bronchoscopy was much greater in the group of patients with tracheobronchitis. Moreover, there was an increased number of extensions of the parenchymal disease in this group, especially when there had been extension of the disease before the procedure. This would suggest the advisability of administering a short course of streptomycin prior to bronchoscopy in all suspected cases of tracheobronchitis in an attempt to control such complications.

6. Streptomycin therapy is a most efficient method of treatment of tuberculous tracheobronchitis.

SUMARIO

La Broncoscopia en un Sanatorio. Repaso de 522 Broncoscopias Consecutivas

1. Preséntase el análisis de 522 broncoscopias.

2. La traqueobronquitis tuberculosa mostró una frecuencia cuádruple en las mujeres, comparadas con los hombres.

3. La atelectasia y los roncos fueron dos veces más frecuentes en las mujeres que en los hombres, indicando esto alguna relación con la presencia de traqueobronquitis tuberculosa.

4. Los bacilos tuberculosos descubiertos por el examen en frotes de las secreciones extraídas broncoscópicamente no deben ser considerados como prueba corroboradora de la existencia de tuberculosis pulmonar a menos que puedan cultivarse también esas bacterias en medios de cultivo.

5. La incidencia de reacciones febriles apreciables consecutivamente a la broncoscopia fué mucho mayor en el grupo traqueobronquítico. Además, hubo en este grupo un número mayor de difusiones de la afección parenquimática, sobre todo si había habido difusión de la dolencia antes del procedimiento. Esto indicaría la conveniencia de administrar una breve tanda de estreptomicina antes de la broncoscopia en todo caso sospechoso de traqueobronquitis con mira a cohibir esas complicaciones.

6. La estreptomicinoterapia constituye un método eficacísimo de tratamiento de la traqueobronquitis tuberculosa.

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BRONCHOGENIC CARCINOMA AND PULMONARY TUBERCULOSIS[1,2,3]

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INTRODUCTION

The coexistence of bronchogenic carcinoma and pulmonary tuberculosis has been a matter of interest to pathologists, internists, and surgeons since 1810 (1). Excellent reviews of the literature concerning case reports, historical aspects, discussion as to the microscopic type of carcinoma, and stage of activity of tuberculosis, as well as diagnostic problems, are well covered by numerous authors (1 through 30).

The frequency of the coexistence of the two conditions is quoted as very infrequent or rare (4, 7). In one series of 4,000 autopsies of which 60 per cent were cases of pulmonary tuberculosis, only one case of coexistence was found (18). In another series of 2,500 autopsies from Sea View Hospital, only 34 cases of primary carcinoma were found coexistent with tuberculosis (22). All the reported series do not agree with this infrequency, for pulmonary tuberculosis is reported to have been found in 9.4 per cent of 138 autopsies in which primary carcinoma of the lung existed (19). In another series of 100 autopsies of primary carcinoma of the lung, 7 per cent were found to have coexisting tuberculosis (17). The writers believe that the coexistence of these two diseases is not so rare as has been previously thought. It is not unreasonable to assume that there are numerous cases which have not been reported. Furthermore, others are probably missed because of failure to perform an autopsy. Either the carcinoma or the tuberculosis can easily overshadow the other in the gross specimen so that selection of tissues for microscopic study must be made with care. Considering the frequency of pulmonary tuberculosis and an increasing incidence of bronchogenic carcinoma, the coexistence of the two diseases should be found more and more frequently. It is not known whether the association of the two is purely coincidental and is no more rare than other unrelated diseases (9, 23) or whether each may even predispose to the other (11, 24, 28). Nevertheless, the present trend of the peak of tuberculosis mortality and morbidity, especially among men, to move into the older age groups is well known (25, 31) and makes even more reasonable the suggestion that the frequency of the coexistence of pulmonary carcinoma and tuberculosis will increase. It is reasonable to believe that, as diagnostic acumen improves, a higher percentage will be diagnosed earlier or at least ante mortem.

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[2] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

[3] Read before the Texas Tuberculosis Association, San Angelo, Texas, September 25, 1948.

The various factors in the diagnosis of coexisting pathology are more readily understood if one can make the diagnosis of the single entity in a patient when such entity clinically resembles the other. In addition to the presentation of 3 cases of coexisting pulmonary tuberculosis and carcinoma in the present report, there will also be presented 2 cases of carcinoma which simulated tuberculosis and one case of tuberculosis which resembled carcinoma.

CASE REPORTS

Coexisting Pulmonary Tuberculosis and Carcinoma

Case 1. J. M., a 53-year-old white male, was admitted to the Veterans Administration Hospital, Legion, Texas, March 6, 1948, complaining of fever, cough, and expectoration of bloody and foul sputum of one month's duration.

On February 16, 1948 he had a sudden chill and temperature of 103°F. A cough which had been chronic for many years became worse and productive of mucoid sputum. Cough and fever persisted with the expectoration becoming foul-tasting and consisting of blood and firm, grayish plugs. The average amount of sputum produced was about 30.0 cc. daily.

Pulmonary tuberculosis was diagnosed with sputum positive for tubercle bacilli in 1923 and again in 1927. Tuberculous laryngitis was also found in 1927. A roentgenogram of July 27, 1927 (figure 1A) revealed large cavities in the upper third of the *right* lung. The patient left the hospital against medical advice. No apparent difficulty was noted in the twenty years from 1927 to 1947, when he stopped working because of fatigue and cough with expectoration. For many years he had been troubled with "pleurisy pains" associated with drawing sensations over the left chest. There was no previous history of weight loss.

On admission the findings were negative with the exception of temperature 100°F., pulse 120, and physical signs indicative of a consolidated area in the *left* apical region. The total leukocyte count was 22,100 per cu. mm. with 81 per cent neutrophils. A chest roentgenogram of April 26, 1948 (figure 1B) showed progressive excavation of the left upper lobe, as indicated. No change was noted in the right apex.

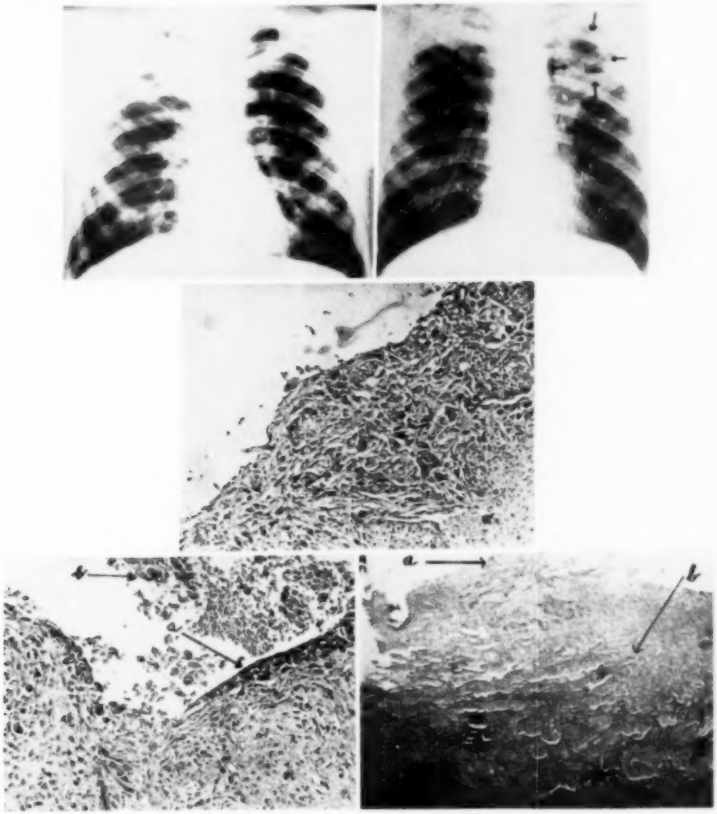
Bronchoscopy on April 2, 1948 revealed some posterior displacement of the left upper lobe orifice with approximately 50 per cent narrowing in its caliber. The mucosa was not remarkable. The cytology of the bronchial secretion was reported as "suspicious for malignancy."

A repeat bronchoscopy on April 12, 1948 revealed the same findings plus reddening of the mucosa in the left stem bronchus. Bronchial aspirations of the second bronchoscopy were negative for malignant cells. Four concentrated specimens of sputum were negative for acid-fast bacilli. The therapy board recommended left upper lobe resection for the then diagnosed left upper lobe abscess. Left total pneumonectomy was performed on May 3, 1948. It was planned to do a left upper lobe lobectomy but the first branch of the pulmonary artery to the left upper lobe was torn at its origin and it was necessary to proceed with a left total pneumonectomy.

Examination of the gross surgical specimen revealed a coarsely nodular and firm apex containing a 5.2 by 3.0 cm. fluctuant cavity, the wall of which was composed of firm, grayish tissue. The mucosa of the bronchus to the left upper lobe was ulcerated with a basal layer of firm, grayish tissue. The parenchyma of the upper lobe was studded with grayish nodules measuring up to 0.6 cm. in diameter. The bronchial tree and the parenchyma of the lower lobe grossly were not remarkable. Microscopy revealed involvement of the left upper lobe bronchus, parenchyma, and cavity by squamous cell carcinoma, Grade III (figures 1C and 1D). Coexistent fibroid tuberculosis was found along the inferior border of the upper lobe. Sections taken from the cavity in the left upper lobe revealed no tuberculosis. The left lower lobe showed extensive fibroid tuberculosis but no neoplastic disease.

The patient's postoperative course was complicated by repeated attacks of acute cardiac

failure and by profound shock, with signs of increasing cerebral irritation. He died eleven days following surgery.



FIGS. 1A–1E. Case 1. Bronchogenic carcinoma and pulmonary tuberculosis

FIG. 1A (Upper left). July 27, 1927. Three large cavities in the upper third of the right lung, the largest measuring 6 cm. in diameter.

FIG. 1B (Upper right). April 26, 1948. Large excavation in left upper lobe, as indicated. No cavitation could be ascertained in the infiltration of the right apex.

FIG. 1C (Center). Microphotograph of section of bronchus from *left* upper lobe, showing replacement of mucosa and underlying structures by squamous cell carcinoma. × 100.

FIG. 1D (Lower left). Microphotograph of section of the cavity of the *left* upper lobe, demonstrating carcinomatous lining (a) and carcinoma cells within the cavity (b). × 100.

FIG. 1E (Lower right). Microphotograph of section of coexistent carcinoma (a) and tuberculous infiltration (b), *right* upper lobe.

Essential post-mortem examination findings: (*1*) Acute adhesive pericarditis (no organisms found); (*2*) tuberculous cavity in *right* apex and fibroid type of tuberculosis through

right middle and lower lobes; (3) squamous cell carcinoma, Grade III, found around the cavity in the *right* upper lobe; (4) squamous cell carcinoma, Grade I, of the prostate.

It seemed unquestionable that the carcinoma of the bronchus was primary and not metastatic from the prostate because the cellular appearance and different growth pattern with ulceration of the bronchus made the original diagnosis quite accurate. Confirmation of this formulation was obtained from the Army Institute of Pathology.

Studies of sections from both upper lobes revealed *only* carcinoma in the left upper lobe, whereas coexistent carcinoma and tuberculosis were present in the right upper lobe (figures 1C through 1E).

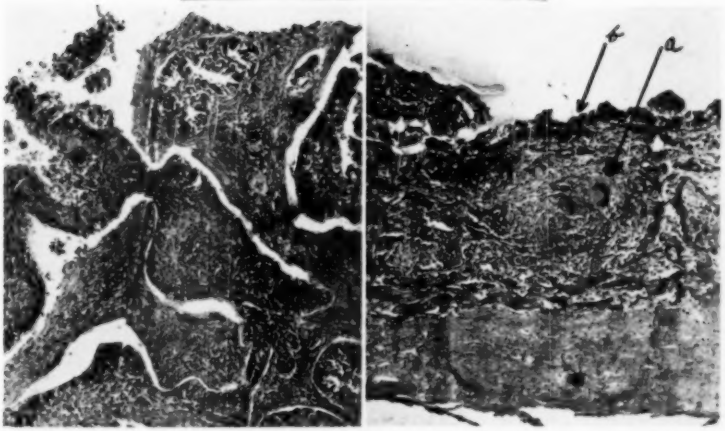
Thus, the patient had had a primary carcinoma arising in the left upper lobe bronchus with resultant cavitation. The tuberculous cavity in the right upper lobe was lined with carcinoma cells and a fibroid type of tuberculosis was found in all other lobes.

Case 2. K. M., a 57-year-old white male, was admitted to Veterans Administration Hospital, Legion, Texas, September 8, 1946 with a history of intermittent chest pains since 1919. At the time of admission he stated that during the previous year and a half he had lost 30 pounds in weight and also had occasional bouts of hemoptysis associated with a chronic cough and shortness of breath.

Physical examination: The patient was chronically ill and markedly emaciated. Increased fremitus was noted over the left lower lobe and dullness to flatness over the left lung below the third rib and sixth dorsal spine. The breath sounds were decreased in the lower half of the left lung with scattered, medium-coarse rales persisting on inspiration after coughing. The clinical impression at the time of admission was pulmonary tuberculosis. A roentgenogram of the chest on September 12, 1946 (figure 2A) revealed almost total destruction of the left lung. Twelve other chest films over the period of his hospitalization revealed no material change.

Chest pains persisted after admission and blood-tinged sputum was produced occasionally. From the date of admission to February 26, 1947 one positive report of acid-fast bacilli in the sputum was filed. Between that date and June 18, 1947, when another smear positive for acid-fast bacilli was recorded, eight smears were reported as negative for acid-fast bacilli. From June 18, 1947 until the date of death, there were thirteen additional "negative" smears for acid-fast bacilli. Five sputum specimens were positive for fungus of the Rhizopus type. Bronchoscopies performed on October 2, 1946, December 4, 1946, and November 7, 1947 revealed gradual diminution in the caliber of the left stem bronchus, with ulceration and roughening of the mucosa. Biopsy material obtained on each of these procedures was "negative for malignancy." An axillary lymph node submitted for microscopic study was "negative for malignancy." The patient developed a left empyema and the aspirated fluid was positive for acid-fast organisms and pneumococci. Intercostal tube drainage was instituted. Shortly thereafter the patient began to have persistent bleeding interspersed with massive hemorrhages, both by trachea and through the drainage tube. Supportive measures in an attempt to prepare the patient for surgical exploration were unsuccessful. Open drainage of the left empyema was performed on November 19, 1947 and tissue obtained by biopsy from the lower border of the presenting lung was reported to show a "chronic inflammatory reaction." The chest pains persisted and the patient was subjected to numerous intermittent pulmonary hemorrhages. His condition gradually became worse, and he expired on April 11, 1948. His massive hemorrhages occurred so frequently that surgical intervention was impossible.

Essential post-mortem examination findings: (1) Pulmonary tuberculosis, with numerous



FIGS. 2A-2C. Case 2. Bronchogenic carcinoma and pulmonary tuberculosis

FIG. 2A (Top) September 12, 1946. Revealed mediastinal shift to the left. The right lung shows slight haziness in apex. Left lung reveals infiltrations with multiple annular shadows in the first and second interspaces. A fluid level within a 5 cm. cavity is present in the third interspace. The remainder of the left lung is a dense homogenous shadow.

FIG. 2B (Lower left). Microphotograph of section of left upper lobe bronchus, showing complete replacement by squamous cell carcinoma. × 100.

FIG. 2C (Lower right). Microphotograph of section of left upper lobe, showing tuberculosis with giant cell formation (a) and carcinoma (b). × 100.

cavities in the left upper lobe and proliferative tuberculosis in the right upper lobe; (*2*) mixed tuberculous empyema, left, with open drainage; (*3*) bronchogenic carcinoma, Grade III (squamous cell), arising at the origin of the left upper lobe bronchus (This carcinoma invaded the entire lumen of the cavity in the inferior part of the left upper lobe); (*4*) no carcinoma was noted in the hilar nodes.

Studies of sections from the left upper lobe revealed replacement of the bronchus by squamous cell carcinoma, carcinomatous metaplasia of the lining of the cavity wall, and coexistent active tuberculosis (figures 2B and 2C).

This is a case of pulmonary tuberculosis with secondarily infected tuberculous empyema in which bronchogenic carcinoma was found at autopsy.

Case 3. S. E., a 50-year-old salesman, was admitted to Veterans Administration Hospital, Legion, Texas, on December 12, 1947 complaining of a pulmonary hemorrhage which occurred six days prior to admission.

Pulmonary tuberculosis had been diagnosed at the Veterans Administration Hospital, Excelsior Springs, in November 1946.

Physical examination after admission of December 12, 1947 was essentially negative except for the chest examination and an old left leg supracondylar amputation for Buerger's disease. On auscultation, wheezing rales and harsh breath sounds were heard throughout both lung fields. Six sputum examinations from December 16, 1947 to April 22, 1948 were all positive for acid-fast bacilli. The therapy board recommended routine care and that patient be considered as a terminal case. Cardiac decompensation present at the time of admission was controlled by digitalization. An electrocardiogram revealed evidences of an old anterior myocardial infarction which was assumed to have been secondary to marked arteriosclerosis. In three months of hospitalization there was considerable increase in the pulmonary tuberculosis. A roentgenogram on March 16, 1948 revealed bilateral, far advanced tuberculosis with cavitation (figure 3A). The patient became more toxic, his respiratory distress increased, and he expired on May 13, 1948.

Essential post-mortem examination findings: (*1*) Bilateral caseopneumonic tuberculosis with numerous cavities; (*2*) squamous cell carcinoma, Grade II; *right* lower lobe with metastasis to hilar lymph nodes; (*3*) coronary occlusions, multiple, with infarctions, old; (*4*) obliterative pericarditis.

It is of interest that a careful dissection of the various bronchial branches of the right lower lobe did not reveal any areas that could be definitely chosen as the beginning of the carcinoma. The carcinoma was found on routine microscopic sections of the lobe.

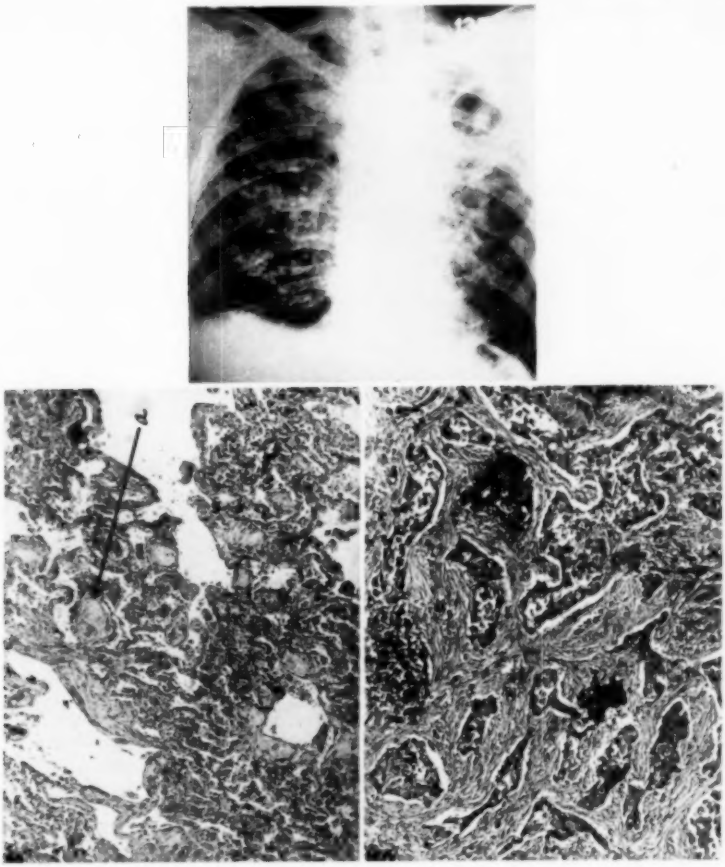
Studies of sections from the parenchyma of the right lower lobe revealed discrete and confluent areas of keratinizing squamous cell carcinoma, with metastasis to the right hilar lymph nodes (figures 3B and 3C).

In this case of far advanced tuberculosis, carcinoma of the lung was found at autopsy.

Pulmonary Tuberculosis which Resembled Bronchogenic Carcinoma

Case 4. W. E. G. was a 35-year-old white male who was admitted to Veterans Administration Hospital, Legion, Texas, on November 7, 1947 with a 10-month history of pains in chest, frequent "colds," occasional night sweats, and increasing weakness. He gave no history of weight loss.

Approximately eight months after his return from Japan, a right upper lobe infiltration and cavitation were found. At John Sealey Hospital, Galveston, Texas, numerous sputum and gastric lavages were negative for acid-fast bacilli. Bronchoscopy was negative. Right pneumothorax was attempted but abandoned because of adhesions, and a thoracoplasty was recommended. Observation at Veterans Administration Hospital, Temple, Texas, in 1947 failed to establish the diagnosis of pulmonary tuberculosis. Patient produced no sputum and six gastric lavages were negative for acid-fast bacilli. The tuberculin test in the first strength was negative and in the second strength was one plus. Bronchoscopy revealed



FIGS. 3A–3C. Case 3. Bronchogenic carcinoma and pulmonary tuberculosis

FIG. 3A (Top). Reveals the replacement of the majority of the left upper lobe by cavity formation and infiltration throughout remainder of the left lung. The entire right lung is the site of a similar infiltration. There is nothing unusual about the infiltration in the right lower lobe.

FIG. 3B (Lower left). Microphotograph of section of right lower lobe reveals squamous cell carcinoma with keratinization (a). (50).

FIG. 3C (Lower right). Microphotograph of sections of carcinomatous metastasis to right hilar lymph node. × 100.

exuberant tissue at the right upper lobe orifice. Examination of material from this area was reported to show "inflammatory tissue."

The patient was then transferred to Veterans Administration Hospital, Legion, Texas, on November 7, 1947. On admission, the essential findings were unimpressive and were

limited to distant breath sounds above the third and fourth ribs on the right. The patient did not appear acutely ill, was well developed, and offered no complaints.

A roentgenogram on admission, December 8, 1947 (figure 4A), revealed an area of increased density in the upper third of the right lung. There was no tracheal deviation. Seven routine smears and three concentrates of sputum were negative for acid-fast bacilli. Bronchoscopy on November 9, 1947 showed no abnormalities. Culture and smears of material aspirated from the right upper bronchus were negative for acid-fast bacilli and malignant cells. Temperature, pulse, and respirations were within normal limits. In view of the numerous negative sputums, it was felt that there was a neoplasm in the right upper lobe. Exploratory thoracotomy was recommended and was performed on December 10, 1947. During the surgical procedure a right apical cavity, measuring approximately 2 cm. in diameter was inadvertently uncapped, and from the appearance of the tissue it was believed that it was probably tuberculous. Only the upper lobe was removed. Immediate examination of the specimen failed to reveal any condition indicative of carcinoma, and the photograph of the specimen (figure 4B) demonstrates typical tuberculosis.

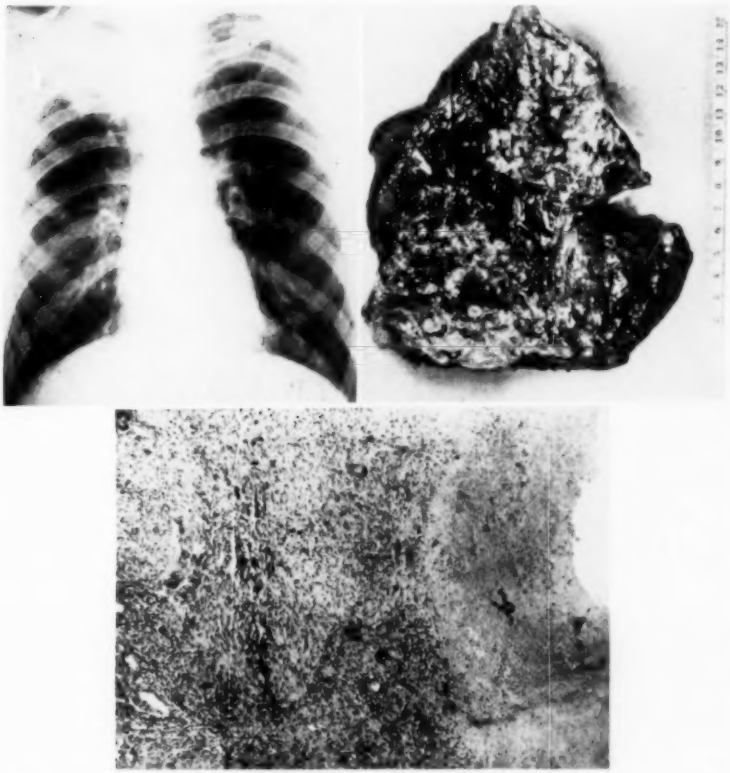
The patient made an uneventful recovery. Three weeks postoperatively, two out of five concentrated routine and certified specimens of sputum were positive for acid-fast bacilli. The patient was placed on a regimen of streptomycin for sixty days. Three 24-hour concentrates of sputum were then negative for acid-fast bacilli. Postoperative bronchoscopy revealed good closure and healing of the right upper lobe bronchial stump. Gross and microscopic examination of the surgical specimen revealed caseating type of tuberculosis surrounded by a peripheral zone of intense fibroblastic proliferation (figures 4B and 4C).

This case is an example of tuberculosis which was not detected bacteriologically and which presented a sufficiently suggestive picture of pulmonary carcinoma so that surgical exploration was performed.

Bronchogenic Carcinoma Resembling Pulmonary Tuberculosis

Case 5. In January 1947, W. F. S., a 51-year-old white male, developed a sharp, right, lower anterior chest pain which lasted for about three weeks and was associated with a productive cough. Early in June 1947, he had an attack of left lower chest pain which was diagnosed as pleurisy. He was admitted to the Valley Baptist Hospital, Harlingen, Texas, on July 19, 1947 and remained there until August 20, 1947, during which time he began vomiting and continued to vomit from one to three times daily. On August 7, 1947, he developed intractable hiccoughing. Roentgenograms made there were reported as showing cavitation in the right upper lobe. Sputum examinations were negative for acid-fast bacilli. He was transferred to the medical chest service of Brooke General Hospital on August 21, 1947. The cavitation of the right upper lobe was noticed at the time of admission (figure 5A), and he had persistent hiccoughing with every respiration and complained of anorexia and nausea. Scattered coarse rales were present throughout both lung fields, especially over the right upper lung anteriorly. A gastrointestinal roentgenographic examination was made and reported to be negative. On September 20, 1947 he began to complain of burning sensations of head, neck, arms, hands, and feet. An electrocardiogram showed nothing unusual. A laminagraph was taken August 25, 1947 (figure 5B) and revealed no distortion of the left stem bronchus or of its immediate divisions. A bronchoscopic examination was done on September 19, 1947 mainly because of the enlarged left hilus noted on the admission film (figure 5A). Nothing abnormal was seen except considerable secretion in the orifice of the bronchus to the right upper lobe. This secretion was aspirated and sent to the laboratory for cultures for acid-fast bacilli, for fungi, and for examination for malignant cells. The bronchial secretions were negative for malignant cells, and cultures were implanted for fungi and for acid-fast bacilli. The patient continued to complain of a burning sensation of the head, neck, arms, hands, and feet. A neurological consultation was obtained and no definite diagnosis could be made. The neurologists stated that the com-

plaints did not follow any dermatomes, nor was there any definite pattern that could be compatible with any organic neurological lesion. Nevertheless, a fungus infection of the brain was considered to be a possibility. A spinal tap was performed and the fluid was



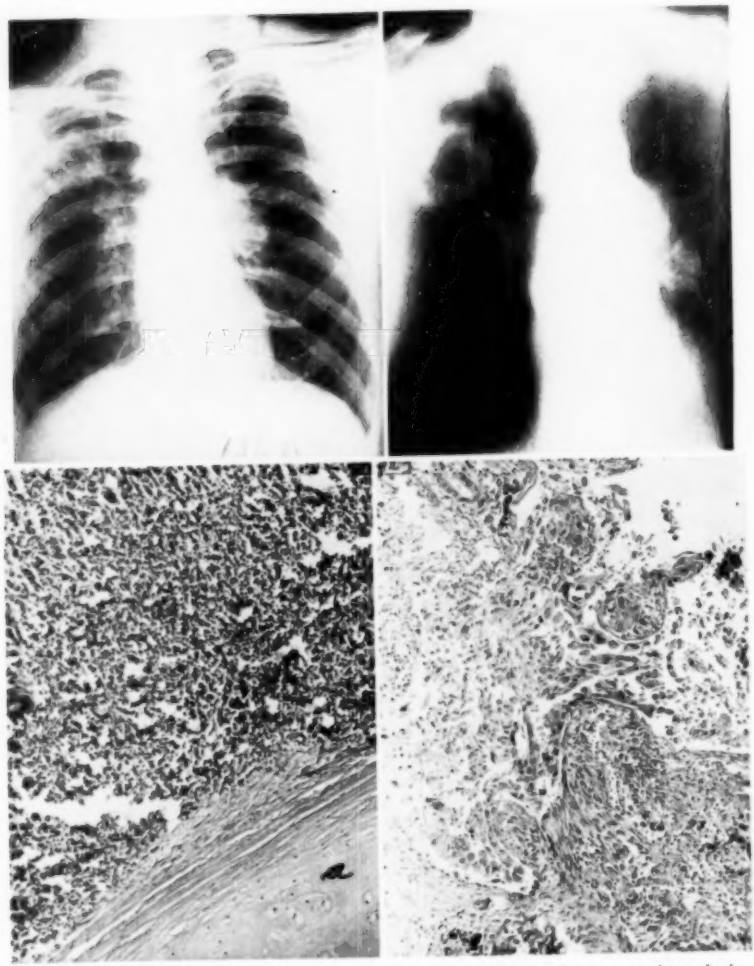
FIGS. 4A–4C. Case 4. Pulmonary tuberculosis resembling bronchogenic carcinoma

FIG. 4A (Upper left). December 8, 1947. Reveals an area of increased density in the upper third of the right lung. There is no tracheal deviation.

FIG. 4B (Upper right). Sagittal section of right upper lobe revealing proliferative and caseating tuberculosis.

FIG. 4C (Bottom). Microphotograph of section of right upper lobe showing both proliferative (a) and caseating (b) tuberculosis. × 100.

crystal clear and under normal pressure. The cell count was 23 leukocytes, of which 22 were lymphocytes and one was a neutrophil. The total protein was 47 mg. per 100 cc. and the sugar was 75 mg. per 100 cc. No abnormal globulin was present and no pedicle formed. The colloidal gold curve was entirely normal. The patient had about 25 sputum concentrates examined during the whole hospitalization and all of these were negative for acid-fast bacilli. A guinea pig injected with sputum failed to develop tuberculosis. Several



FIGS. 5A–5D. Case 5. Bronchogenic carcinoma resembling pulmonary tuberculosis

FIG. 5A (Upper left). August 25, 1947. Cavitation *right* upper lobe with enlarged *left* hilus.

FIG. 5B (Upper right). August 5, 1947. Laminagraph (12 cm.) reveals a cavity in the right upper lobe and the lower part of left stem bronchus with its divisions unchanged.

FIG. 5C (Lower left). Photomicrograph of section of anaplastic carcinoma, left stem bronchus, adjacent to bronchial cartilaginous ring (a). × 100.

FIG. 5D (Lower right). Photomicrograph of section of carcinoma of the right upper lobe cavity wall. × 100.

sputum examinations revealed the same type of fungus. These were sent to the Army Area Laboratory for identification and were tentatively identified as *Candida Krusei*, a non-pathogenic strain of monilia. The patient required considerable narcotics for his burning sensations. He never would admit complete relief of the burning from any drug that was tried. Early in October 1947 he developed an asthmatic type of respiration and moderate swelling of the ankles. Values for the blood protein and albumin-globulin ratio were normal. The kidney function was within normal limits. He was digitalized on an empirical basis with fairly prompt disappearance of the edema and improvement in respiration. The patient's complaints continued and became more frequent in regard to the burning sensation. Sedation was gradually increased until the patient was in almost constant narcosis but with very little relief. All medications were then discontinued and the patient was given a series of intravenous procaine drips which were also ineffectual. Axillary nodes had been removed from both axillary regions and had been negative for malignancy or sarcoidosis. The patient suddenly expired December 15, 1947 from a massive pulmonary hemorrhage.

Essential post-mortem examination findings: (*1*) Bronchogenic carcinoma, arising in the left upper lobe bronchus, anaplastic with lymphatic spread; (*2*) carcinoma, metastatic with cavitation, right upper lobe; (*3*) metastatic carcinoma involving medulla oblongata, diaphragm, pancreas, and pulmonary regional lymph nodes.

Studies of sections revealed an extensive anaplastic type of bronchogenic carcinoma with widespread metastasis (figures 5C and 5D). There was no evidence of tuberculosis in any of the pulmonary lesions.

Case 6. J. T., a 55-year-old male, was first admitted to Veterans Administration Hospital, Legion, Texas, on January 8, 1934, complaining of pain in the left chest, dry cough, loss in weight, night sweats, and bouts of increasing temperature.

In his past history he claimed he had been discovered to have pulmonary tuberculosis in 1919 and to have sustained a pulmonary hemorrhage in 1931. No other information as to where the diagnosis was made and whether or not he underwent treatment for the pulmonary hemorrhage is available from the records.

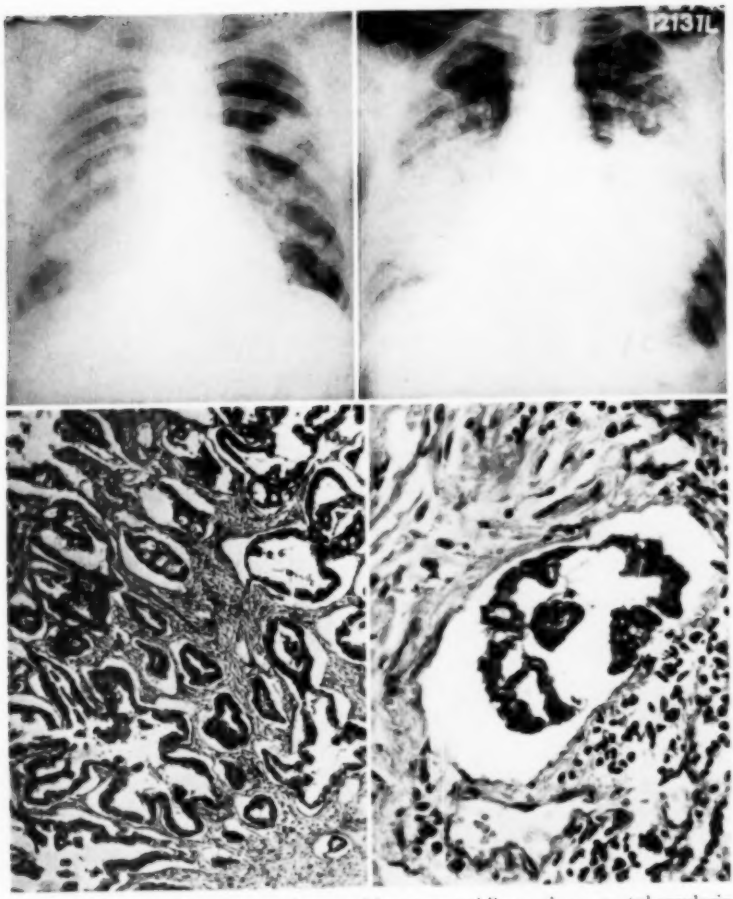
During the period of hospitalization in 1934, the established diagnosis of pulmonary tuberculosis (chronic, inactive) was based on roentgenographic evidence and physical findings. Review of this film revealed questionable evidence for this diagnosis. There was only a slight increase in bronchial marking in the right upper lobe region. Eight certified sputum specimens taken at that time were all reported negative for acid-fast bacilli. He was discharged after nine days of hospitalization.

He returned to the hospital on May 16, 1946, claiming he had been well and working until three months before admission. In the period immediately prior to admission he had "streaking" in the mornings, and noted dyspnea, fatigability, and loss of 27 pounds. A roentgenogram made on May 20, 1946 (figure 6A) revealed an opacity in the medial portion of the right lung with patchy areas of opacities throughout the left lung. A series of seven single and three concentrated specimens of sputum were negative for acid-fast bacilli. The patient left the hospital against medical advice after thirty-four days, refusing further diagnostic procedures and the discharge diagnosis was "pulmonary pathology, etiology undetermined."

He re-entered the hospital on February 26, 1948, complaining of increasing weakness, weight loss, and a nonproductive cough, all of which had been getting progressively worse since 1946. Three weeks prior to admission, his dyspnea became severe. Fever was noted a few days prior to admission.

On admission he was in marked respiratory distress associated with cyanosis. The temperature was 99°F., the pulse 120, the respiration 40 per minute, and the blood pressure 90 systolic and 70 diastolic.

Physical examination revealed an acutely ill male with rapid and labored respirations,



FIGS. 6A–6D. Case 6. Adenocarcinoma of lungs resembling pulmonary tuberculosis

FIG. 6A (Upper left). May 20, 1946. Opacity in the lower third of the right lung with patchy areas of opacities throughout the left lung.

FIG. 6B (Upper right). February 27, 1948. Marked bilateral generalized infiltrations coalescing into solid opacities in lower halves of both lung fields.

FIG. 6C (Lower left). Photomicrograph of section of right lower lobe showing adenocarcinoma. × 100.

FIG. 6D (Lower right). Photomicrograph of section of right lower lobe showing carcinoma in lymph channel. × 430.

showing a distinct cyanosis. A roentgenogram of February 27, 1948 (figure 6B) revealed a marked bilateral generalized infiltration coalescing into solid opacities in lower halves of both lung fields.

The patient was in extremis upon admission and expired six days after admission.

Essential post-mortem examination findings: (*1*) Adenocarcinoma of lungs with metastasis to liver and spleen (The primary site was in the parenchyma of right lower lobe); (*2*) lymphogenous metastatic spread of carcinoma.

Studies of sections revealed pulmonary adenocarcinoma with lymphogenous spread involving pulmonary parenchyma (figures 6C and 6D) and visceral organs.

This case is one of the infrequent pulmonary carcinomas with lymphogenous spread resulting in a roentgenographic appearance of tuberculosis.

DISCUSSION

The problem of whether pulmonary tuberculosis may be responsible for the initiation of a primary carcinoma has been a subject of considerable discussion and is brought to mind in Cases 1, 2, and 3. The various phases of metaplasia in the breakdown and healing process of tuberculosis should facilitate the development of cancer (2, 3, 28). In all of the first 3 cases the tuberculosis was present for long periods before the presumed onset of the cancer. The development of carcinoma in a tuberculous cavity or in a tuberculous scar has been reported (3, 6, 8). It has been pointed out that careful study reveals that cancer cells found in a tuberculous cavity have not originated there but in a bronchial wall and have ultimately invaded the cavity (11). This is felt to be the situation in Case 3. This is in line with the feeling that all primary cancers of the lung arise from various portions of the bronchi (12, 26, 27, 14). Other writers, however, (16, 20, 21, 15, 13) report carcinomas which they believe arose from "alveolar epithelium" of the pulmonary alveoli.

As cancer is a debilitating disease, it can be complicated by an exacerbation of a pre-existing, smoldering tuberculosis (9). It is of interest from the standpoint of immunology that, in a few of the reviewed cases (11) in which active tuberculosis developed subsequent to carcinoma, the tuberculosis remained confined to the lung involved by the tumor. It is possible that in these cases the organisms released were the so-called "immured" type. The question has also been discussed as to whether extensive active tuberculosis is antagonistic to the development of primary carcinoma of the lung. No support for this possibility was obtained from the present series nor are there any cases reported which do more than suggest the possibility.

A case has been reported (5) of extensive pulmonary tuberculosis in which a "small cell infiltrating carcinoma was found starting from the bronchial wall, spreading through the lung along the lymph vessels and the bronchi, and produced the picture of a carcinomatous pneumonia and lymphangitis." This is an excellent description, except for cell type, of Case 6 in which the roentgenogram resembled a florid tuberculosis.

The detection of cancer in a patient with a positively diagnosed tuberculosis is difficult because reasons for even suspecting a coexisting condition are few indeed. Evidences of carcinoma are usually obscured by the tuberculosis. Cough, expectoration, bloody sputum, pain, loss of weight, and secondary anemia are so common in tuberculosis that to suspect another disease one has to be unusually astute and constantly on the alert. Roentgenographic densities produced by

tuberculosis are so heterogeneous, resembling every roentgenographic change of carcinoma that, even with the autopsy report at hand, it is difficult and often impossible to detect error in the original reading of the roentgenogram. In Case 4 the roentgenographic appearance is similar to numerous bronchogenic carcinomas which have been seen either clinically or at the autopsy table. This fact plus the numerous sputums and gastric lavages which were negative for acid-fast bacilli made exploration imperative. The negative sputums might in a sense be explained by the remarkable amount of proliferative reaction around all of the caseating foci. It is important to realize, with the roentgenographic picture in mind, that the right upper lobe bronchus and its immediate branches were not the site of any tuberculosis. Reviewing this case with the diagnosis made from the surgical specimen, it is believed that in light of present-day diagnostic methods one is justified in proceeding with surgical exploration in such a case. There is nothing pathognomonic in such a history nor in such a roentgenogram. In contrast to Case 4 were the findings in Case 6, wherein the roentgenographic densities resembled a florid, rapidly advancing tuberculosis, with negative diagnostic laboratory tests. It is well recognized that, if laboratory findings are contrary to the clinical picture, the result of the laboratory test should not be too strongly considered. This practice is a result of experience with cases of tuberculosis which may not at first have sputum positive for tubercle bacilli, although such evidence is eventually forthcoming. Repeated negative examinations of the sputum, however, have great significance when, from the roentgenographic and clinical picture, one would ordinarily suspect active tuberculosis. In these cases, further diagnostic procedure must go hand in hand with continued search for bacilli in the sputum. It is of interest to realize that approximately a year and nine months elapsed between roentgenograms (figures 6A and 6B) and it is reasonable to assume the carcinoma was widespread at the time the first roentgenogram (figure 6A) was taken.

An analysis of some of the symptoms and findings previously enumerated can be of help. A change in the character of the cough as elicited in a careful history may result in the information that it has at the same time become more frequent and harassing but actually less productive. A tuberculous stenosis that would lessen the amount of sputum does not as a rule cause a cough to become more frequent and harassing. The type of sputum is not helpful. Massive hemoptysis is more common in tuberculosis than in carcinoma. The presence or absence of tubercle bacilli does not exclude carcinoma but bloody sputum in the absence of tubercle bacilli in patients in the fifth and sixth decade is presumptive evidence of carcinoma. The fact that the sputum was negative for tubercle bacilli on the last admission in Case 1 did not give much cause for concern because it is frequently difficult to obtain "positive" sputum in fibroid tuberculosis or in old tuberculous stenotic bronchial lesions. In Case 2, with all of the tuberculosis found at autopsy, it is difficult to understand why there were thirty-eight "negative" examinations of the sputum and only two sputum specimens which were positive for acid-fast bacilli. This is probably a result of the progressive stenosis of the bronchus. It is interesting to speculate as to whether this stenosis was due

to carcinoma from the beginning. If this were so, the carcinoma might well have been present for twenty months or even longer. From clinical experience and published case reports (29), squamous cell carcinoma of the bronchus has been known to be present for much longer periods.

Putrid sputum is more common in carcinoma than in tuberculosis for, although tuberculous cavities can and do become secondarily infected, the abscesses distal to carcinomas are more frequently encountered. Thus in Case 1 it was felt that a putrid abscess had developed distal to an old tuberculous bronchial stenosis, for nothing in the range of the bronchoscope could be seen, such as ulceration or tumefaction. Only one of the two bronchial smears was considered to be suspicious of cancer. A left upper lobe lobectomy had been planned but, due to a technical mishap, the "proper therapy" was performed. The term "proper therapy" is used in this case only in the sense of proper degree of resection. It is difficult enough to differentiate between an abscess secondary to bronchogenic carcinoma and an abscess due to other causes, without having the picture further clouded with a previously diagnosed pulmonary tuberculosis.

The pain of tuberculosis is usually the result of involvement of the pleura and, if there is added the deep, boring, usually relentless pain unrelated to the phase of respiration, carcinoma may be suspected. In Case 2, on the basis of the persisting pain, the question of carcinoma was considered. Not much weight was given this consideration, however, for it was believed that the progressive bronchial stenosis with its distal suppuration could cause the hemorrhages, and insufficient attention was given to the pain. In Case 3, there was nothing in the history or course of events while the patient was in the hospital to lead one to believe that it was other than a far advanced case of tuberculosis. This case is not put forth as a mistaken diagnosis but one in which carcinoma was an incidental and accidental finding. The only symptoms of significance present were pain and dyspnea. Pain, as in the other cases, was not carefully enough described to be of aid in diagnosis except for the fact, as mentioned previously, that it was not of the pleuritic type.

The dyspnea in Case 3 was thought to be caused by the cardiac condition and such an assumption was probably correct. In considering dyspnea, it should be remembered that dyspnea out of proportion to the visible lesion of the lung usually means carcinoma and, when present, is a bad prognostic sign. Dyspnea, especially if it is increasing or paroxysmal without apparent cause, if often significant of carcinoma. Dyspnea is seen in extensive tuberculosis, especially with the commonly associated emphysema. The combination of increasing pain and dyspnea out of proportion to the remainder of the clinical picture should cause one to investigate further. Both continuing loss of weight and anemia are only of importance in arousing suspicion when they occur in the face of adequate therapy for the tuberculosis. These symptoms are especially significant when they continue with no unusual changes in the roentgenogram.

The areas of tuberculous infiltration and segmental atelectasis are indistinguishable by roentgenogram. The atelectasis as seen on a conventional film might either be due to the carcinoma or to tuberculous bronchial involvement.

Occasionally some help can be obtained in distinguishing between an atelectasis secondary to carcinoma of a bronchus and tuberculous bronchial infiltration by the use of laminagrams to observe the type of distortion of the outlined air column. To state that such an involved bronchus is due to carcinoma or tuberculosis is again difficult. If the carcinoma has not been present long, however, the chances are that, if a considerable segment of the bronchus is involved, it is more likely to be due to tuberculosis than to carcinoma. Furthermore, it is not to be forgotten that what was assumed to be tuberculous stenosis with lymph node involvement occasionally can be shown by laminagraphy to be a mass surrounding a bronchus and extending out from it without any true bronchial stenosis.

When first presented at surgical chest conference, it was assumed that the cavitation in the right upper lobe in Case 5 would eventually be proved to be tuberculous but it was believed that the enlargement of the left hilar area demanded further investigation. Bronchoscopy and bronchial smears failed to reveal any carcinoma. The presence of carcinoma was still considered to be a possibility, however, and, in order to visualize the branches of the left stem bronchus beyond that seen by the bronchoscope, laminagraphs were taken and no narrowing or distortion was seen at that time. Had these been repeated two or three months later, at least a proper diagnosis could have been made. The severity of this patient's neurological symptoms made his management most difficult. This case, then, presented originally the findings of tuberculosis in the right upper lobe. The contralateral hilar enlargement was investigated even before the many "negative" sputum reports had been received because it was believed that an enlarged hilum on a tuberculosis basis would of necessity be a mass of nodes draining a parenchymal lesion and there was no evidence of any such lesion in the left upper lobe.

All of the above are merely generalizations which should arouse suspicion so that further diagnostic work might be instituted. In the routine examination of sputum for tuberculosis, a cough plate of fresh material can be examined for malignant cells. It is well recognized that visualization of the tumor mass and examination of material obtained by biopsy are the best methods for establishing a positive diagnosis. Although bronchoscopy was apparently performed on three different occasions in Case 2, including an examination approximately six months before death, no carcinoma was seen. In stenosing lesions of the left upper lobe bronchus, the resultant atelectasis often narrows and distorts the left stem bronchus so that it is often difficult, and sometimes impossible, to reach the level of the origin of the left upper lobe bronchus. When the tumor is not within reach of the bronchoscope, bronchial smears and, better still, hemotoxylin and eosin stains of paraffin sections of centrifuged material aspirated from a bronchial lavage may frequently demonstrate cancer cells.

SUMMARY

Three cases of coexisting bronchogenic carcinoma and pulmonary tuberculosis are reported. In addition, 2 cases of bronchogenic carcinoma simulating tuberculosis and one case of tuberculosis resembling bronchogenic carcinoma are also presented.

It is suggested that an increasing frequency of combined bronchogenic carcinoma and pulmonary tuberculosis may be expected.

The possibilities of each of the pathological entities acting as an etiological factor in the production or exacerbation of the other is discussed.

The diagnostic difficulties created by the presence of the combined processes are presented.

SUMARIO

Carcinoma Broncógeno y Tuberculosis Pulmonar

Al presentar 3 casos de carcinoma broncógeno y tuberculosis pulmonar coexistentes, agréganseles 2 casos de carcinoma broncógeno simulando tuberculosis y 1 caso de tuberculosis semejando carcinoma broncógeno.

Señálase que cabe esperar una frecuencia creciente de carcinoma broncógeno combinado con tuberculosis pulmonar.

Discútense las posibilidades de que cada una de dichas entidades patológicas actúe como factor etiológico en la producción o exacerbación de la otra.

Repásanse las dificultades con que tropieza la valuación de los síntomas y hallazgos en presencia de ambos procesos combinados.

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RELATIONSHIPS BETWEEN TUBERCULOSIS AND BRONCHIECTASIS[1]

A Study of Clinical and of Post-mortem Material

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INTRODUCTION

The literature contains many excellent clinical and pathological descriptions of bronchiectasis, including several attempts to assess the relationship between this condition and pulmonary tuberculosis. Norris and Landis (1) stated that more than 21 per cent of tuberculous lungs seen at autopsy exhibit bronchiectasis. Recently Riggins (2) has presented a summary statement for bronchiectasis in general; in particular, he has pointed to enlarged tuberculous tracheobronchial lymph nodes as a likely cause of bronchial obstruction and the resulting bronchiectasis. Eloesser (3), in describing bronchial stenosis in the tuberculous lung, gave two illustrations showing marked bronchiectasis distal to the stenotic area in cases in which a barium-gelatin mixture had been injected post mortem. Brock *et al.* (4) have suggested that obstructive lesions which give rise to the shadow characteristic of lobar or segmental consolidation at times eventuate in bronchiectasis. A typical case history was presented. More recently Kent (5) pointed to a number of children who had developed bronchiectasis in areas of former "atelectasis." Dormer and his associates (6–10) in South Africa have suggested that the complication of bronchiectasis is very common and often is of such clinical moment as to overshadow the tuberculosis and render collapse ineffective. In the latter study, however, one may question: (a) the degree of selection represented by their material, (b) the accuracy of bronchograms alone in demonstrating bronchiectasis in lungs already distorted by chronic disease, and (c) the clinical implications of the observations presented in their well-illustrated, interesting papers.

Bronchiectasis in Primary Tuberculosis

A report made in 1942 (11) showed that approximately 12 per cent of children hospitalized with the diagnosis of tuberculosis exhibited dense, homogeneous, roentgenographic shadows due to pulmonary consolidation. Bronchoscopic examination demonstrated that in three-fourths of these cases the consolidation was associated with various degrees of bronchial obstruction, the latter being caused by edema; tuberculous inflammatory or ulcerative processes of the bronchial wall; thick, bronchial secretions; or by encroachment upon the lumen from the pressure caused by enlarged tracheobronchial lymph nodes. In several instances clearing of the roentgenographic shadow of consolidation followed promptly upon re-establishment of the bronchial airway.

In the above study no particular attempt was made to determine the sequelae

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of such bronchial obstruction, although in 2 cases bronchiectasis was demonstrated. Stimulated by this latter observation, an effort was made to bring children in this group back to the sanatorium, along with other similar cases, and to obtain bronchograms of the former diseased area in each case. Altogether, 37 children were so studied and have been reported upon elsewhere in detail (12). All of the patients had had primary tuberculosis. Their mean age was five and one-half years, with extremes of two years and twelve years. The instillation of lipiodol (12) was made at a mean interval of three and one-half years after roentgenographic clearing of the pulmonary lesion. In 3 of the 37 patients it was not possible to instill lipiodol in the area of former disease. One of these 3 subsequently underwent lobectomy which revealed total obstruction of the bronchus by an adenoma rather than a tuberculous lesion, along with extensive bronchiectasis distal to the obstruction. Zavod (13) has presented an excellent technique for this type of study.

Among the 34 children with satisfactory bronchograms, definite bronchiectasis was found in 24. Twenty of these patients with bronchiectasis had shown evidence of bronchial obstruction for longer than one year; the remaining 4 had shown such evidence for less than twelve months. Of the 10 patients who showed no bronchiectasis, 5 had had the obstruction twelve months or less and 5 for longer than twelve months.

Bronchiectasis was distributed equally between the lungs; 12 children showed the lesion in the right lung and 12 in the left. Localization was conspicuous in the anterolateral branch of the upper lobe bronchus (9 cases), the apical branch of the lower lobe bronchus (4 cases), and in the middle lobe bronchus (4 cases). The lingula escaped in this series of children—a fact of some interest because this portion of the lung is commonly involved in so-called reinfection tuberculosis.

The 34 satisfactory bronchograms mentioned above had been preceded by bronchoscopic examination in 26 children. Bronchiectasis occurred in 13 who had shown tuberculous bronchial lesions and in 5 whose bronchi appeared anatomically normal. Among the 8 without bronchiectasis in whom bronchoscopic examination had been made, 6 had had tuberculous bronchial lesions and 2 had had apparently normal bronchi.

The location and type of bronchial affection appeared to be related to subsequent bronchiectasis. The bronchiectasis tended to be coextensive with the bronchus and cylindrical from root to periphery. This led to the assumption that anatomical or physiological obstruction from endobronchial disease at or near the root or from enlarged tracheobronchial lymph nodes are the responsible factors.

In respect to the question of the congenital origin of bronchiectasis in these cases, it is believed that tuberculosis would scarcely locate in every instance at the seat of a congenital bronchial lesion. Furthermore, during the obstructive period, tubercle bacilli were demonstrated in 33 of the 34 children studied. This leaves no doubt as to the acquired nature of these bronchial lesions.

The symptoms produced resolved themselves into two categories, namely, those associated with the obstruction and primary complex, and those resulting

from the subsequent dilatation. In the first group, symptoms were variable in degree and kind; wheezing was by far the most common, with bouts of fever, cough, and thick sputum frequently present as well. As the primary disease receded, symptoms became correspondingly less prominent. Surprising as it may seem, only one child has been left with symptoms severe enough to require attention. Pneumonectomy was recommended for this patient's illness. In the others, to date the ectasia has been relatively silent and unobtrusive with but few of the characteristic recurrent "colds," repeated attacks of pneumonitis, fever, cough, copious expectoration, or hemorrhage. The frequent location of the lesion in only one bronchial branch may account for this paucity of symptoms or, possibly, secondary infection may become apparent only after a greater period of time has elapsed.

One case history is cited to illustrate the type of result obtained from the bronchogram.

Case 1: D. R. a Negro girl, seven years of age on admission, experienced an abrupt onset of symptoms December 3, 1941, consisting of headache, feverishness, epistaxis, and anorexia followed by a dry cough but no wheezing. Ten days later a chest roentgenogram revealed disease, and the skin reaction to tuberculin was positive. The patient was admitted to Maybury Sanatorium December 31, 1941. At that time she was pale, tired, and anemic, with low-grade fever as high as 100°F. Initial sputum, stool, and gastric cultures were all negative for tubercle bacilli, but the roentgenogram of the chest showed extensive lymph node enlargement at the right hilum and an area of parenchymal consolidation confined strictly to the lateral segment of the middle lobe (figures 1 and 2). These findings were interpreted as indicating the presence of primary tuberculous infection. On January 28, 1942, bronchoscopic examination showed a moderate amount of secretion in the right main bronchus, with the mucous membrane reddened and edematous.

In March 1942, the patient developed transitory pleural effusion on the right, associated with a fever of 104.6°F. Tubercle bacilli were cultured from the fluid. Following this episode, the anterolateral segment of the right upper lobe became consolidated (figures 3 and 4) and tubercle bacilli were present on culture of gastric material. Resolution of the parenchymal lesions progressed slowly but was complete by December 17, 1944, when the patient was discharged. Previous to her departure, a bronchogram was made. This showed bronchiectasis confined to the lateral segment of the middle lobe, with unsatisfactory filling of the upper lobe.

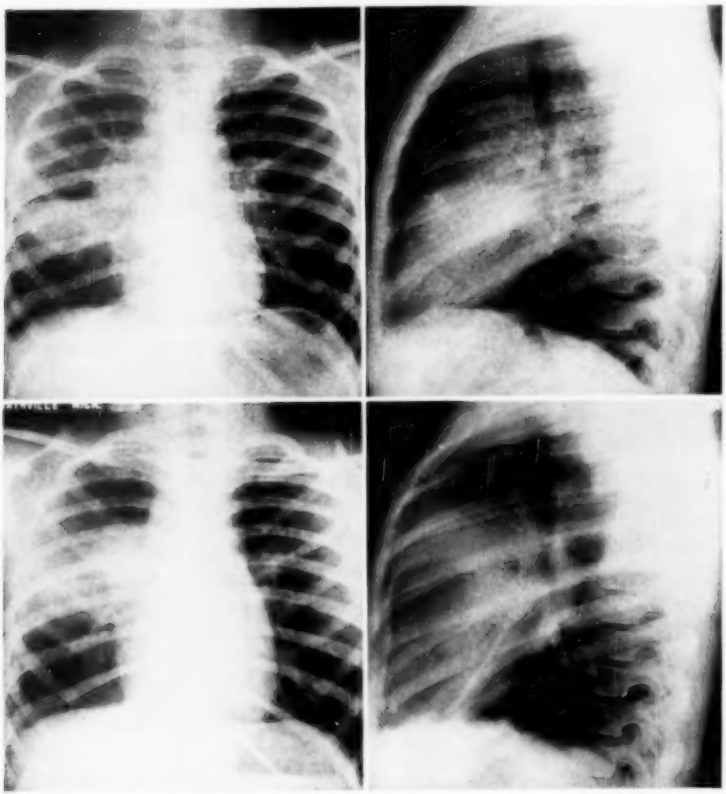
In July 1947 the patient, well during the intervening two and one-half years, was readmitted in order to check the status of the bronchial tree. A roentgenogram taken at this time showed only slight residual scarring in the formerly diseased segments of the middle and upper lobes (figure 5). Bronchiectasis was demonstrated in both the lateral segment of the middle lobe and the anterolateral segment of the upper lobe, however, and the process was more severe in the former and where consolidation had been of longer duration (figures 6 and 7).

OBSERVATIONS ON REINFECTION TUBERCULOSIS

Bronchiectasis as Revealed in Post-mortem Material

It appears well established that primary tuberculosis is frequently followed by bronchiectasis. During the course of these observations on children, an extension of the study seemed feasible in an attempt to ascertain the relationship between reinfection tuberculosis and bronchiectasis. Autopsy material was chosen since it permitted a histological confirmation of the accuracy of the

bronchographic evidence and permitted the study of consecutive cases. On the other hand, it must be recognized that changes in dying patients may not be



FIGS. 1–4. Case 1: (Upper left) Admission roentgenogram (December 31, 1941) showing lymph node enlargement on right and consolidation of lateral segment of middle lobe.

(Upper right) Lateral view (December 31, 1941).

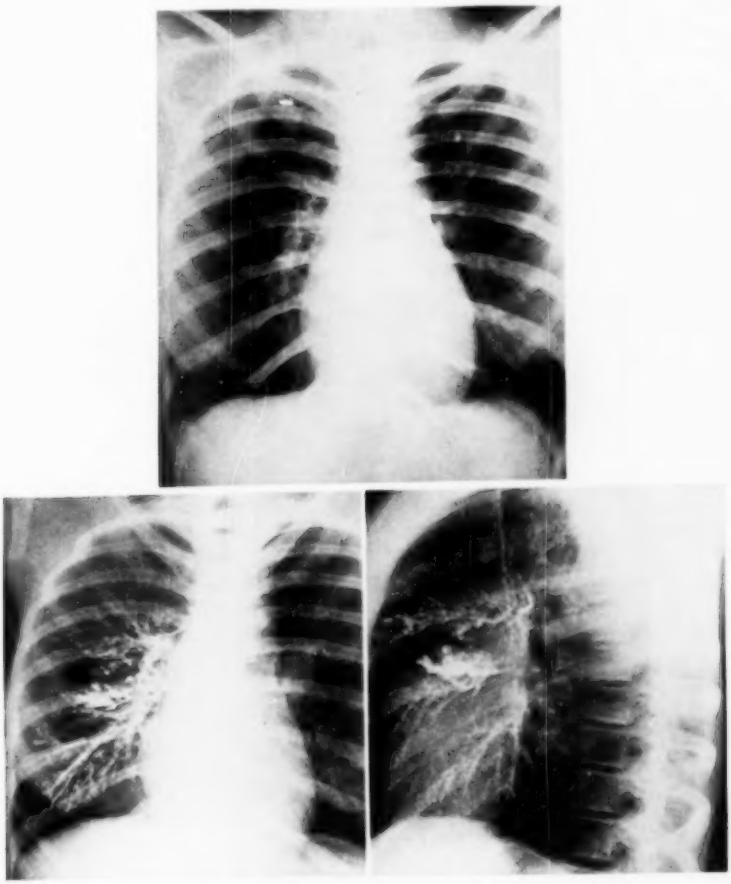
(Lower left) Roentgenogram of October 13, 1942, showing consolidation of anterolateral segment of right upper lobe.

(Lower right) Lateral view (October 13, 1942).

entirely representative of the usual status of the lesion during life. Accordingly, due allowance for this possible element of selection must be made.

Materials and methods: A technique for injecting the lungs post mortem was devised. Hill's mass as used by Birkelo and Brosius (14) for injecting the pulmonary vascular system was suggested by them for injecting the bronchial tree, and the following formula, modified slightly as shown below, proved satisfactory.

40 per cent solution of gum acacia in 10 per cent formalin	100 cc.
Bismuth oxychloride	20 Gm.



FIGS. 5–7. Case 1: (Top) Readmission film just prior to bronchogram (figures 6 and 7).

(Lower left) Bronchogram of July 29, 1947 showing bronchiectasis in lateral segment of middle lobe and anterolateral segment of upper lobe.

(Lower right) Lateral view (July 29, 1947).

The lungs were removed *en masse* at the autopsy table by extrapleural dissection, and the tracheobronchial tree was lavaged thoroughly to free it of sputum and blood. In order to ensure complete filling of the bronchial tree without alveolar obliteration, the radiopaque mass was injected under fluoroscopic control and a roentgenogram made immediately.

After the specimen had been in formalin for a few days, a meticulous dissection was made

with the bronchogram as a guide, special attention being given to those portions of the lung where the mapping suggested bronchiectasis or had been incompletely filled. Careful search was made for bronchial stenosis or other abnormality of possible pathological significance. Blocks of tissue for histological section were taken from all suspected areas. The sections were stained with hematoxylin and eosin and many were stained for elastic tissue and tubercle bacilli.

TABLE 1

Bronchiectasis as Found post Mortem in the Lungs of Tuberculous Patients

Positive histologically, positive by bronchogram	46
Positive histologically, negative by bronchogram	9
Negative histologically, positive by bronchogram	5
Negative histologically, negative by bronchogram	40
Total	100

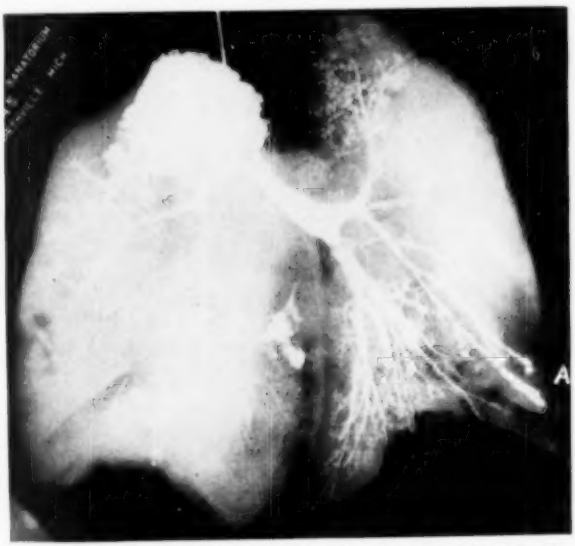


FIG. 8. Post-mortem bronchogram showing questionable bronchiectasis (A). Description given in text; case history not presented.

Incidence and characteristics of bronchiectasis: In this manner material from 100 unselected and nearly consecutive autopsies on tuberculous patients was studied, all but one of whom were reinfection cases. Among this number there were 51 instances in which post-mortem bronchogram alone demonstrated bronchiectasis. In 46 cases this diagnosis was substantiated by gross examination and histologic study. As indicated in table 1, a fairly close correlation existed between roentgenographic and histological results. There were, however, several notable discrepancies; for example, in figure 8 the structures labeled "A" in the lingula were interpreted as bronchiectasis, whereas the histologic section

showed merely spaces lined by necrotic debris. No remnants of the bronchial wall could be found.

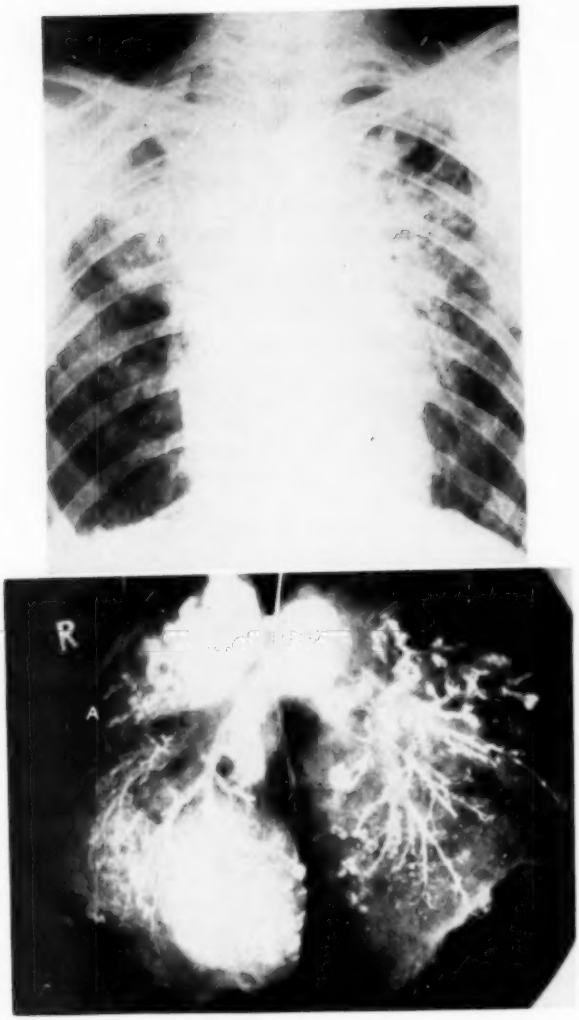
This illustrates the destructive type of disease which often followed the course of the bronchial tree, leaving merely a cavity bounded by caseous material and surrounded in turn by collapsed alveoli. All gradations were found between this extreme and instances of typical bronchiectasis lined by stratified, squamous epithelium and showing minimal destructive changes. Most commonly, however, tuberculous disease in the wall was extensive, at times causing some difficulty in identification of the bronchial wall itself. Because of these variations, it was felt that the incidence of bronchiectasis should be based on those cases where the diagnosis was validated by all methods of examination. As indicated, the incidence by these criteria was 46 per cent.

The incidence of bronchiectasis varied with the type of tuberculous lesion. In those cases with predominantly fibrotic disease (49 cases) the incidence rose to 65.3 per cent and, conversely, in those with predominantly exudative lesions (36 cases) it dropped to 19.4 per cent.

In like manner development of bronchiectasis was related to the age of the tuberculous lesion. From the history it was possible to establish the duration of disease in 74 instances with considerable confidence. In 19 cases in which disease was regarded as less than one year old, bronchiectasis was found only twice; once as a result of extrinsic pressure on a bronchus, and once in a fulminating tuberculous lesion known to be less than three and one-half months old. One-half of the lesions of two years' duration had bronchiectasis, whereas this incidence remained essentially unaltered in the groups of older lesions. It appeared, therefore, that bronchiectasis in reinfection tuberculosis was most apt to occur after the first year of disease when the lesion had largely lost its exudative quality. Extreme chronicity did not seem to materially increase the chance for development of bronchiectasis. The observations of Pinner (15) and of Boyer (16) in so-called fibroid phthisis also indicated that there is a higher incidence of bronchiectasis in this type of disease.

In the bulk of cases there existed certain similarities in configuration. The dilatations were both saccular and cylindrical, but more commonly the latter. They were apt to be multiple but, nevertheless, were limited in extent and were distributed largely in accordance with the parenchymal lesion. Thus, predilection was shown for the upper lobes and the apical ramifications in the lower lobes. Characteristically, dilatations were confined often to peripheral areas in striking contrast to bronchiectasis associated with primary tuberculosis. There was no sharp limitation in respect to bronchopulmonary segmentation, and oftentimes localized dilatations were seen in three or four unrelated segments. Although bronchiectasis could be demonstrated in a large percentage of cases, it seemed probable that in the majority it was so limited in extent as to have had little bearing on the clinical course. The most notable exceptions were in patients with bronchial stenosis and in those who had had extensive collapse procedures.

The following is given as an example of the ante-mortem and post-mortem observations in one case.



FIGS. 9-10. Case 2: (Top) Admission film.

(Bottom) Post-mortem bronchogram showing localized bronchiectasis on the right (A) and cylindrical or coextensive bronchiectasis on the left (B).

Case 2: The patient, J. H., was a white male 33 years of age. The onset of illness, with cough and expectoration, began two and one-half years before admission. Shortly thereafter he was rejected by his draft board but refused hospitalization. Gradual loss of weight ensued and a few weeks before admission cough and weakness increased rapidly. The patient

entered Maybury Sanatorium with far advanced pulmonary tuberculosis and sputum for *M. tuberculosis*. A roentgenogram revealed dense areas of infiltration involving the upper half of both lungs, and less dense areas throughout the remainder. There was bilateral cavitation, more marked on the right as illustrated in figure 9. The patient's course in the sanatorium was progressively downward; tuberculous meningitis developed, and he died five months after admission.

The lungs were removed extrapleurally and injected intratracheally as described above. The bronchogram (figure 10)[3] showed extensive cavitation and, in the area marked A, there were small but definite areas of localized bronchiec-

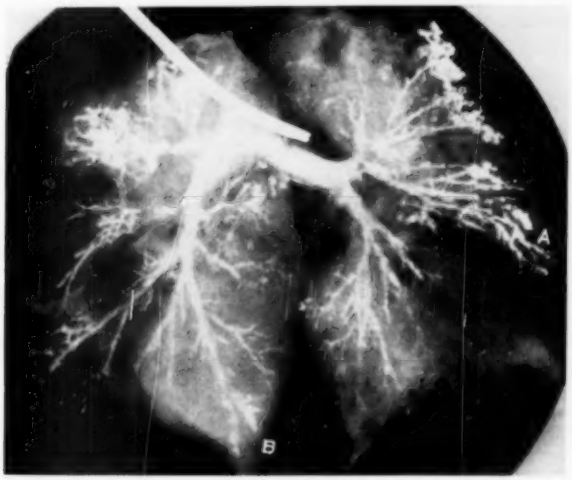


FIG. 11. Post-mortem bronchogram showing bronchiectasis (A and B). Case history not presented.

tasis adjacent to the cavity. On the left, the anterolateral and posterolateral branches of the upper lobe bronchus (marked B) were distinctly dilated throughout, as in the bronchiectasis found in primary tuberculosis. Dissection revealed the presence of large fibrocaseous lymph nodes which nestled around these dilated branches at their origin, providing a possible etiological explanation for the genesis and type of ectasia.

DISCUSSION

Bronchiectasis following primary tuberculosis results from disease in the bronchi at or near the root or from enlarged tuberculous tracheobronchial lymph nodes which encroach upon the bronchus. These processes tend to set up bronchial obstruction. Dilatation, therefore, tends to extend from root to periphery.

[3] Typical peripheral bronchiectasis is shown better in figure 11, A and B, from another case.

In reinfection tuberculosis the affection is characteristically limited in extent and occurs in the area of the tuberculous disease. It usually involves only small, isolated, peripheral segments. Frequently it is multiple and occurs in several lobes, the distribution corresponding to the distribution of the parenchymal lesions and thus occurring mostly in the upper lobes. In 3 cases bronchiectasis was extensive and it was suspected that strategically placed tuberculous lymph nodes which were found at the root may have caused "blocking off" at the time of the primary lesion many years before (Case 2). Obstructive lesions in smaller bronchi were encountered occasionally (eight times) and were associated with localized peripheral dilatation.

A good case can be made for bronchial obstruction as the etiological factor in the type of bronchiectasis associated with primary tuberculosis, i.e., cylindrical dilatations, coextensive with the bronchus from root to periphery and conterminous with bronchopulmonary segmentation. Moreover, the process is often sufficiently distinctive to allow for identification as "post-primary" bronchiectasis on the basis of configuration alone. We have found useful application of these observations by repeatedly demonstrating bronchiectasis in adult patients in the area of healed primary disease, particularly in those cases where scarring or distortion is seen in the neighborhood of the calcified primary complex. We offer this as a roentgenological sign of some clinical importance.

In contrast to the findings with primary tuberculosis, the factors leading to bronchiectasis in reinfection tuberculosis were less tangible. They may be discussed under the following categories:

Bronchial occlusion: Where bronchial stenosis was present, distal dilatation was profound and the relationship obvious, but these cases constituted a small minority. It is possible that in the remaining cases transient obstruction may have occurred during the course of the disease, and this may have favored development of the dilatations. Careful study of the specimens, however, produced no evidence to support such a contention.

Extrinsic factors: The surrounding parenchymal lesions were sometimes fibrotic, with distortion of anatomical details. In these cases it is conceivable that "extrinsic factors" may have been responsible, or, at least, participant in producing the dilatations as indicated by numerous authors. It was significant, however, that in all but 2 or 3 cases destructive changes were invariably present in the walls themselves, suggesting that dilatation was not caused exclusively by external "tug." Many times there was little evidence of retraction or distortion to suggest an "extrinsic factor" in the development of the ectasia.

Intrinsic factors involving the bronchial wall: Changes were invariably present in the wall of the bronchus itself. In the milder cases this consisted in loss of elastic tissue with lymphocytic infiltration. More often, however, destructive changes were marked, with extensive involvement of the wall by tubercles and caseation. Usually the musculature was largely destroyed and often difficult to identify; often cartilage was damaged and epithelium denuded or metaplastic. Evidence of repair was frequently lacking, and the process in these cases suggested devolution into simple tuberculous cavity. McNeil and associates (17), studying

the lungs of children who died following ordinary bronchopneumonia, have made observations somewhat similar to the above. In their cases also marked destruction of the bronchial wall was present, the resulting lesion being described as "bronchiectatic cavities." According to these authors, such bronchiectatic cavities may heal by granulation, with fibroblasts and capillaries forming a granulation tissue membrane enclosing the space which subsequently re-epithelizes. The possibility presents itself that conceivably tuberculous bronchiectasis could develop in a similar manner. Rilance and Gerstl (18) visualized the processes as consisting of: (*1*) involvement of the bronchus by destructive tuberculous disease, (*2*) excavation of this "granuloma", and (*3*) subsequent re-epithelization. Obviously, associated bronchial obstruction or distortion from surrounding fibrotic, parenchymal disease would promote the process but might not be requisite for the creation of bronchiectasis in reinfection disease.

Tannenberg and Pinner (19) were unable to produce bronchiectasis experimentally unless both infection and obstruction were present. These observations appear to be applicable to the clinical conditions described above as occurring in primary tuberculosis.

CONCLUSIONS

1. Bronchiectasis develops with surprisingly high incidence in the wake of primary tuberculosis. In 34 children with obstructive pneumonitis associated with primary infection, 24 were found to have definite dilatation.

2. Bronchiectasis associated with primary tuberculosis tends to be coextensive with the bronchus and extends from root to periphery. In the cases studied the dilatations conformed precisely to the segmental structure of the tracheobronchial tree, deriving from bronchial obstruction at the root.

3. Bronchiectasis arises in association with reinfection tuberculosis in approximately 50 per cent of fatal cases. It is localized and patchy and corresponds to the distribution of the tuberculous lesion.

4. Post-mortem injection of the air passages with radiopaque material offers an excellent way of determining bronchial dilatation.

5. In such material most of the bronchi which are dilated are actually the seat of tuberculous disease.

CONCLUSIONES

Relación entre la Tuberculosis y la Bronquiectasia. Estudio de Material Clínico y Autópsico

1. La bronquiectasia muestra una frecuencia sorprendente por lo alta a continuación de una tuberculosis primaria. De 34 niños con neumonitis oclusiva asociada a infección primaria, 24 mostraron dilatación bien definida.

2. La bronquiectasia asociada a tuberculosis primaria suele coincidir en su extensión con el bronquio: se extiende de la raíz a la periferia. En los casos estudiados, las dilataciones conformáronse precisamente a la estructura segmentaria del árbol traqueobronquial, partiendo de la obstrucción bronquial en la raíz.

3. La bronquiectasia se presenta en asociación con la tuberculosis de rein-

fección aproximadamente en 50 por ciento de los casos letales. Localizada y esparcida en placas, corresponde a la distribución de la lesión tuberculosa.

4. La inyección *post mortem* de las vías aéreas con una sustancia radioopaca proporciona un excelente modo de determinar la dilatación bronquial.

5. En el material así obtenido, la mayor parte de los bronquios dilatados son en realidad asiento de enfermedad tuberculosa.

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THE DISSEMINATION OF TUBERCLE BACILLI IN EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG[1]

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INTRODUCTION

The dissemination of tubercle bacilli in experimentally infected guinea pigs was first studied by Arloing (1). This preliminary work was later investigated by Oehlecker (4), Griffith and Griffith (2), Krause (3), and Willis (6). In general, these workers agreed that tubercle bacilli spread rapidly through the body of infected guinea pigs. Their findings suggested that the rate of spread of the bacilli varied from twenty-four hours to four days. None of these workers, however, made detailed histologic, biologic, or microscopic examinations of all, or even of the more important, organs.

The aim of this investigation was to determine the time at which the tubercle bacilli reach various organs in experimentally infected guinea pigs, the channels by which the bacilli were disseminated, and the time taken for the development of lesions.

TECHNIQUE AND MATERIALS

The three groups of guinea pigs used were designated A, B, and C.

Group A consisted of 24 guinea pigs which received tuberculous material taken from a tuberculous guinea pig infected with 0.01 mg. of human-type (H37Rv). The spleen and lymph nodes from the tuberculous guinea pig were emulsified and 1.0 ml. of the resultant suspension was inoculated subcutaneously into the thigh of each animal in the group. The number of bacilli inoculated was not known but, judging by the smears, the inoculum contained a small number of tubercle bacilli. Human-type tubercle bacilli were used in this part of the investigation.

Group B consisted of 32 guinea pigs and Group C of 70 guinea pigs. All of these animals were inoculated with a culture of a bovine strain of tubercle bacilli which had been isolated from a cat. The culture was weighed and emulsified. The animals of Group B were inoculated subcutaneously with 1.0 mg. of this suspension, whereas the members of Group C received 0.3 mg. per guinea pig.

Certain animals in each of these three main groups were killed at intervals after inoculation which ranged from one hour to twenty-one days. Each guinea pig was subjected to a detailed *post-mortem examination* and biologic, histologic, and microscopic examinations were then performed.

Before each guinea pig was killed, it was bled into a tube containing approximately 3 mg. of potassium oxalate per ml. The plasma and corpuscles were then separated and the corpuscles lysed. The plasma and the lysed corpuscles were then inocu ated separately into the guinea pigs. After death, urine was collected from each guinea pig and the centrifuged deposit was inoculated into another guinea pig. In one case, feces were used in place of the urine. The precrural, inguinal, popliteal, and sublumbar lymph nodes and the spleen, liver, lungs, kidney, bone marrow, and brain were removed in as aseptic a manner as possible and placed in sterile Petri dishes. Portions of lymph nodes, spleen, liver, kidneys, and lungs from Group C were then taken and placed in 5 per cent formalin and the remaining

[1] From the Department of Veterinary Pathology, University of Liverpool, Liverpool, England.

tissues were placed in individual mortars and emulsified. The suspensions of each organ were then inoculated into healthy young guinea pigs. Prior to making an emulsion, smears were made from each organ and examined for acid-fast bacilli.

The guinea pigs which were inoculated with emulsion of the various organs were killed as soon as they showed gross enlargement of the lymphatic nodes on clinical examination. Animals which showed no gross lesions after three months were killed.

RESULTS

Group A. Animals infected with bacilli of the bovine type: In the group A animals the inguinal, precrural, sublumbar, and popliteal lymph nodes, together with spleen and blood, were examined for the presence of tubercle bacilli. The guinea pigs were killed and their organs subinoculated[2] at intervals which ranged from twenty-four hours to twenty-two days from the beginning of the experiment. Acid-fast bacilli were present in the lymph nodes at twenty-four hours, and in the spleen between forty-eight and ninety-six hours, after subcutaneous inoculation. The blood did not show the presence of tubercle bacilli until the twenty-second day after inoculation. The results are summarized in table 1.

TABLE 1

Dissemination of Human-type Tubercle Bacilli in Guinea Pigs (Group A)

ORGANS	TIME AFTER WHICH ORGANS WERE EXAMINED FOR THE PRESENCE OF TUBERCLE BACILLI					
	24 hours	48 hours	4 days	8 days	14 days	22 days
Lymph nodes	+	+	+	+	+	+
Spleen	−	−	+	+	+	+
Blood	−	−	−	−	−	−

+ = Tubercle bacilli present as proved by guinea pig inoculation.
− = No evidence of tubercle bacilli.

Group B. Animals infected with 1.0 mg. bovine-type bacilli: The guinea pigs in Group B were sacrificed at intervals which ranged from sixteen to ninety-six hours after initial inoculation. The same tissues were then examined as were examined in the Group A animals. In addition, the liver was examined in the Group B animals sacrificed at seventy-two hours, and after ninety-six hours the liver, lungs, and kidneys were also examined.

The lymph nodes from animals slaughtered after being infected for sixteen hours all contained tubercle bacilli, as was proved by biologic examinations. The spleen was also shown to contain tubercle bacilli after sixteen hours. Subinoculated guinea pigs, which were inoculated with blood taken from the guinea pigs killed at the sixteenth, forty-eighth and seventy-second hours after infection, all showed generalized tuberculosis. The subinoculated guinea pigs killed three months after inoculation with blood taken from the guinea pigs killed at twenty-four, forty-eight, sixty-four, and ninety-six hours after infection did not reveal any evidence of tuberculosis.

[2] The guinea pigs which were used for biological examination will be referred to as subinoculated guinea pigs.

Specimens of liver removed from the infected guinea pigs after seventy-two or ninety-six hours and from lung and kidney after ninety-six hours produced tuberculosis in subinoculated animals. The results are summarized in table 2.

Group C. Animals infected with 0.3 mg. bacilli of bovine type: In view of the findings in Group A and B, it was decided to examine the tissues from the Group

TABLE 2

Dissemination of Bovine-type Tubercle Bacilli in Guinea Pigs (Group B)

ORGANS	TIME AFTER WHICH ORGANS WERE EXAMINED FOR THE PRESENCE OF TUBERCLE BACILLI						
	16 hours	24 hours	40 hours	48 hours	64 hours	72 hours	96 hours
Lymph nodes	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+
Blood	+	−	−	+	−	+	−
Liver	N.E.	N.E.	N.E.	N.E.	N.E.	+	+
Lungs	N.E.	N.E.	N.E.	N.E.	N.E.	N.E.	+
Kidneys	N.E.	N.E.	N.E.	N.E.	N.E.	N.E.	+

+ = Tubercle bacilli present as proved by guinea pig inoculation.
− = No evidence of tubercle bacilli.
N.E. = Organs not examined.

TABLE 3

Dissemination of Bovine-type Tubercle Bacilli in Guinea Pigs (Group C)

ORGANS	TIME AFTER WHICH ORGANS WERE EXAMINED FOR THE PRESENCE OF TUBERCLE BACILLI						
	1 hour	6 hours	12 hours	24 hours	36 hours	48 hours	96 hours
Lymph nodes	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+
Lungs	+	+	+	+	+	+	+
Kidneys	+	+	+	+	+	+	+
Bone marrow	+	+	+	+	+	+	+
Brain	*	*	−	+	+	*	*
Urine	+	+	+	+	+	+	+
					(Feces)		
Blood	+	+	−	−	−	−	+

+ = Tubercle bacilli present as proved by guinea pig inoculation.
− = No evidence of tubercle bacilli.
* = Died a few days after inoculation.

C animals at earlier times and at shorter intervals than those examined in Group B. The times after inoculation at which the guinea pigs were killed were one, six, twelve, twenty-four, forty-eight, and ninety-six hours. The tissues examined included lymph nodes, as previously, spleen, liver, lungs, kidneys, blood, bone marrow, brain, urine and, in one instance, feces. As may be seen, most of the organs contained tubercle bacilli as soon as one hour after subcutaneous inoculation. The majority of the guinea pigs infected with brain suspension died soon

after inoculation. Generalized tuberculosis was present in 2 of the guinea pigs which had survived inoculation with brain suspension obtained twenty-four and thirty-six hours after infection. No evidence of tuberculosis was found in the guinea pigs inoculated with the brain suspension removed twelve hours after infection. The results are summarized in table 3.

Microscopic Appearance of the Lesions

Spleen: Sections of the spleen removed between one and twelve hours after subcutaneous inoculation of tubercle bacilli showed evidence of early acute congestion. This and other changes were more marked with the Group B guinea pigs, i.e., the ones which had received the largest inoculum. Between twelve and thirty-six hours, the hyperemia became more marked and there was an increase in the number of leukocytes in the vessels. The leukocytes were largely neutrophilic in type, and there were present a few metamyelocytes. At this stage the lymph follicles appeared to be more prominent and were densely packed. The nuclei of the cells were hyperchromatic. Neutrophils and a few histiocytes were scattered through the spleen substance, and there was some inflammatory swelling of the lymph sinuses. Sections stained by the Ziehl-Neelsen method showed a very few histiocytes containing acid-fast bacilli. No extracellular organisms were seen.

Between thirty-six and sixty-four hours after inoculation, the changes were more marked than those noted earlier. There appeared to be more free red cells in the spleen substance, however, and a greater number of neutrophilic leukocytes were present. In general, the spleen had a more cellular appearance. Histiocytes were more frequent in the lymph channels than previously.

At seventy-two hours the first definite lesion was noted (figure 1) and was seen at this time only in Group B guinea pigs. The corresponding lesion was seen in the ninety-six-hour guinea pig of Group C. The tuberculous focus appeared as a lighter-stained area with a very small central area of necrosis. The cells adjacent to the central necrotic area had undergone fatty change. They appeared to be degenerated histiocytes and neutrophils. The bulk of the lesion was composed of neutrophils, many of which had undergone or were undergoing degeneration. A few early fibroblasts were present at the periphery of the lesion.

At ninety-six hours in the Group B spleens the lesions were larger. The central necrotic area had not increased in size, but the area of leukocytic infiltration and the area of dead leukocytes had increased. The predominant cell was still the neutrophil, but a few sparse eosinophils had made their appearance. Fibroblasts were more distinct, and collagen fibers were present at the periphery of the lesion.

The lesion four days after inoculation was much the same except that it had grown by direct extension and, in part, had undergone what appeared to be hyaline change. The necrotic area was still very small. Between seven and twenty-two days in the Group A spleens, the microscopic appearance of the lesion did not vary a great deal. At twenty-two days the lesion was a well-defined tubercle with a central area of necrosis and a few neutrophils. Epithelioid cells were present in large numbers. There was a poor attempt at encapsulation and no giant cells, caseation, or calcification were seen.

Lymph nodes: The changes noted in the chain of lymph nodes were very similar to those seen in the spleen. An early congestion was present and at twenty-four hours there was an infiltration of the cortex of the gland with eosinophils. These changes were not present in all the early sections. At this stage inflammatory

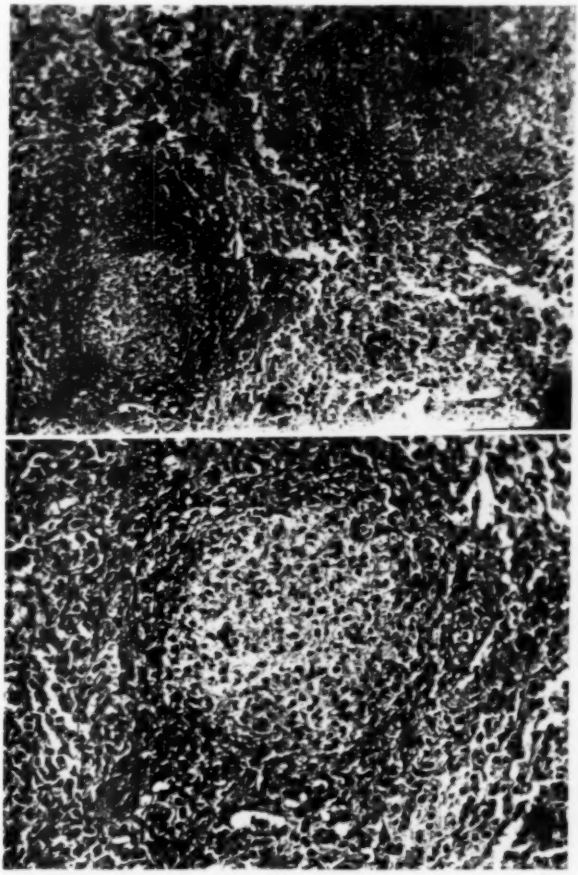

FIG. 1. (Top) Tuberculous lesion in the spleen seventy-two hours after infection. × 100 H&E.

FIG. 2. (Bottom) The same lesion; higher magnification. × 200 H&E

swelling of the lymph channels was also found. At forty-eight hours, the follicles were not so sharply defined, and the lymph nodes were very cellular, with neutrophils prominent in small areas. Free erythrocytes were scattered through the substance of the node. At fifty-six hours, a few slightly paler-stained areas were noted, especially in the region of the neutrophilic concentrations. Microscopic

tubercles were present in the inguinal lymph nodes between sixty-four and seventy-two hours. These resembled the lesions described in the sections of the spleen.

Liver: No changes were noted in the liver (Groups B and C) until after forty-eight hours, when fatty changes became apparent at the periphery of the lobules. The central veins were congested and a few cells in this area had undergone necrosis. Extensive cloudy swelling was present. At sixty-four hours the sinusoids were prominent and the fatty changes more diffuse. Ninety-six hours after infection the liver damage was more severe and the organ showed marked congestion. No acid-fast bacilli could be found in sections stained by Ziehl-Neelsen.

The first tuberculous lesion was noted at four days and consisted of a small focal accumulation of cells, largely neutrophils but with a few histiocytes. The central area of the lesion had undergone necrosis and hyaline change. The cells adjacent to this area did not stain well. At fourteen days the picture was much the same except that the foci were more sharply defined and epithelioid cells were more prominent. Some degree of periportal infiltration with round cells and some bile-staining were found in this area.

Other organs: No gross or microscopic lesions were noted in the other organs obtained from animals sacrificed during the first few days after infection.

DISCUSSION

These experiments showed that tubercle bacilli spread very rapidly in guinea pigs, reaching the lymph nodes and various organs during the first hour after infection. Among the factors concerned in the dissemination of organisms in the body, the number of bacteria inoculated is an important one. When a small dose was inoculated (as in Group A), tubercle bacilli reached the spleen some time between the forty-eighth and ninety-sixth hours after inoculation. In Group B, when a larger dose was inoculated, tubercle bacilli were found in the spleen as early as one hour after infection. Other organs, such as liver, kidney, and lung were also invaded by tubercle bacilli in the same period of time (Group C). The results obtained with brain tissue removed at various intervals from infected guinea pigs were not very conclusive, since many of the subinoculated guinea pigs died. From those which survived, it appeared that the brain was the last organ to be invaded by the tubercle bacilli. Tubercle bacilli were found in the brain twenty-four hours after infection.

Blood regularly contained tubercle bacilli only in the first few hours. This suggested that the blood stream played an important part in the immediate distribution of tubercle bacilli in the body. Subsequently tubercle bacilli appeared in the blood at irregular intervals.

The results obtained from subinoculation with urine and in one case with feces were most interesting. Tubercle bacilli were demonstrated in the urine, as in all other organs, one hour after inoculation. This suggested that tubercle bacilli may be excreted from the body before they are localized in various organs. This has been previously reported by Perla (5) who showed that guinea pigs inoculated

intraperitoneally with tubercle bacilli often excreted the organisms in the feces and in the urine during the first week after inoculation and also during the last stages of the diseases.

Microscopic examination of the various organs showed that the lymph nodes and the spleen were the first organs to show changes which appeared twenty-four hours after infection. The first definite microscopic tuberculous lesion was present in the inguinal lymph node at sixty-four hours, and in the spleen at seventy-two hours, after infection. Cellular changes in the liver appeared at forty-eight hours and the first tuberculous lesion was noted at four days after infection. No gross or microscopic lesions were noted in the other organs in the first few days although the tubercle bacilli were present in these organs. This was probably due to differences in organ susceptibility.

Oehlecker (4) found tubercle bacilli in the iliac lymph nodes, the lungs, and the spleen between the third and the fifth days after subcutaneous inoculation of guinea pigs with a small loop of an emulsion of human tubercle bacilli. Similar results were obtained by Krause (3) who found tubercle bacilli in all of the tissues removed four days after infection. He observed microscopic changes in the various lymph nodes between four and twelve days after infection.

Griffith and Griffith (2) made cultural examinations of organs and the blood of guinea pigs which had received subcutaneous inoculation of tubercle bacilli. They found that tubercle bacilli were disseminated throughout the body within twenty-four hours after infection. The number of organisms in the blood was largest twenty-four hours after infection and the organisms disappeared gradually thereafter.

The results described in this paper confirm the general findings previously reported and in addition provide more detailed information concerning the dissemination of tubercle bacilli in the animal body.

SUMMARY

The dissemination of tubercle bacilli has been examined in guinea pigs infected experimentally with human-type bacilli from tuberculous organs or with a culture of bovine type tubercle bacilli. It was found that, the heavier the inoculum, the greater and the quicker the rate of spread of the bacilli in the body.

Tubercle bacilli were discovered in the majority of the organs one hour after subcutaneous inoculation. The brain appeared to be the last organ invaded. Examinations of the blood revealed that tubercle bacilli were present in the first few hours after inoculation and therafter only at irregular intervals.

The earliest microscopic changes appeared in the lymph nodes and the spleen at twenty-four hours, and in the liver at forty-eight hours, after infection. The first definite microscopic tubercles were present in the inguinal lymph node at sixty-four hours, in the spleen at seventy-two hours, and in the liver at four days after infection. No gross or microscopic lesions were observed in the other organs in the first few days after inoculation.

SUMARIO

La Diseminación de Bacilos Tuberculosos en la Tuberculosis Experimental del Cobayo

La diseminación de los bacilos tuberculosos fué estudiada en los cobayos infectados experimentalmente con órganos tuberculosos y con un cultivo del tipo bovino del bacilo tuberculoso, observándose que, mientras mayor era el inóculo, más intensa y rápida era la propagación de los gérmenes en el organismo.

A la hora de la inoculación subcutánea descubriéronse bacilos tuberculosos en la mayoría de los órganos, siendo aparentemente el cerebro el último órgano invadido. Los exámenes de la sangre revelaron signos de bacteriemia transitoria, pues había bacilos tuberculosos presentes en las primeras horas consecutivas a la inoculación y después sólo a plazos irregulares.

Las primeras alteraciones microscópicas aparecieron en los ganglios linfáticos y el bazo a las 24 horas, y en el hígado a las 48 horas, de la infección. Los primeros tubérculos microscópicos bien definidos estaban presentes en los ganglios linfáticos inguinales a las 64 horas, en el bazo a las 72 horas, y en el hígado a los cuatro días, de la infección, sin que se observaran en los demás órganos lesiones macro- o microscópicas durante los primeros días.

Acknowledgment

The authors wish to express their thanks to Dr. G. O. Davies for his continued interest in this work and to Mr. L. Kelley for his technical assistance.

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STUDIES IN TUBERCULOSIS CHEMOTHERAPY[1]

I. Simple Primary Aromatic Amines, *in Vitro* and *in Vivo*

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The high tuberculostatic power of simple primary aromatic amines was apparently first noted by Kuroya (1). This activity has been studied extensively by Bloch, Erlenmeyer, *et al.* (2, 3, 4, 5, 6) who recognized the generalized high activity of simple aromatic amines, pointed out the specificity of action against the tubercle bacillus, and developed rules relating structure and activity. In particular, they point out the effectiveness of *para* substitution with lipophilic groups in increasing the *in vitro* activity of these compounds.

In the course of an extensive testing program the writers have examined a number of compounds which would appear to be a continuation and expansion of this series. In addition, a number of observations have been made relevant to the application of this class of compounds *in vivo*.

METHODS

In vitro tests: The *in vitro* method used for testing the tuberculostatic action of the compounds is essentially similar to the method published by Youmans (7) in which the subsurface growth of virulent human-type tubercle bacilli was employed. Since that report several modifications in the technique have been made. The method as now used is given below in detail.

Medium: The modified Proskauer & Beck synthetic medium has the following composition:

Asparagin	0.5 per cent
Monopotassium phosphate	0.5 per cent
Potassium sulfate	0.05 per cent
Glycerol (reagent grade)	2.0 per cent
Magnesium citrate	0.15 per cent

The above ingredients are dissolved, in the order given, in water redistilled from glass. Care is taken to dissolve completely each ingredient before the addition of the next and to add the magnesium citrate after the hydrogen ion concentration is adjusted to pH 7.0 with 40 per cent sodium hydroxide. The medium is sterilized by autoclaving at 15 pounds' pressure for twenty minutes. Occasionally a troublesome precipitate has appeared following autoclaving. This has been found to be due to the inadvertent use of too high a temperature, too long a time of sterilization, or to certain batches of magnesium citrate.

Glassware: All glassware is cleaned thoroughly with soap and water, rinsed seven to eight times in tap water and three or four times with distilled water. In the initial studies test tubes measuring 200 by 25 mm. containing 10 ml. of medium were employed but, in order to conserve material and space, test tubes 150 by 20 mm. containing 5.0 ml. of medium are currently used. These tubes are covered with aluminum caps instead of cot-

[1] From the Research Laboratories, Parke, Davis & Co., Detroit, Michigan, and Department of Bacteriology, Northwestern University Medical School, Chicago, Illinois.

ton plugs. The sterilization of all glassware, including pipettes, is done in the autoclave at a pressure of 20 pounds for twenty minutes.

Preparation of drug dilutions: Each drug is studied in a concentration of 10 mg. per 100 cc. Compounds soluble in water are dissolved directly in the synthetic medium. The more insoluble compounds are first dissolved in 1.0 or 2.0 cc. of ethyl alcohol, acetone, ether, propylene glycol, 0.1 molar sodium hydroxide, or 0.1 molar hydrochloric acid, depending on their solubility in these substances. The solutions are then diluted with medium to make a concentration of 10 mg. per 100 cc. If difficulty is still experienced in dissolving a heat-stable substance, it is heated to boiling for five minutes, and the subsequent dilutions are made while the solution is still warm. Those few compounds which would not go completely into solution in any manner at this concentration are filtered to remove any undissolved material, and an estimate made of the amount which did not go into the solution. Ten different concentrations of each drug are prepared from the 10 mg. per 100 cc. concentration by serial dilution, each concentration representing one-half of the preceding one. Separate pipettes are utilized for each dilution. The heat-stable compounds are diluted and sterilized in the autoclave at 15 pounds' pressure for twenty minutes. Heat-labile compounds are filtered through either Berkefeld, sintered glass, or Swinney syringe-type filters, following which they are diluted aseptically.

Microorganism: The virulent H37Rv strain of *M. tuberculosis* var. hominis is employed. Each tube of each drug dilution and appropriate control is inoculated with approximately 0.1 mg. of a fine suspension of this organism. The suspension is prepared by grinding by hand with a sterile pestle in a sterile mortar a portion of a surface pellicle culture which had been grown on the synthetic medium for fourteen to twenty-one days. During the grinding process the culture is diluted gradually with 0.01 molar phosphate buffer solution until a fairly heavy suspension is obtained. This is then transferred to a sterile test tube and allowed to stand at room temperature for thirty minutes. At the end of this time the larger clumps have settled out, leaving a relatively fine homogeneous supernatant suspension. This supernatant suspension is then transferred by decantation to a second sterile tube.

Such suspensions may be standardized in several ways (8). The simplest and most rapid, however, is the centrifugation of an aliquot in a Hopkins vaccine centrifuge tube. Following centrifugation, the packed tubercle bacilli in the tip of the tube can be measured in terms of cubic millimeters and each cubic millimeter arbitrarily assigned a wet weight of 1.0 mg. Following standardization, the suspension is diluted with phosphate buffer so that the inoculum for each tube contains 0.1 mg. The tubes are inoculated by means of a dropping device, in which the desired amount of inoculum is contained in one or two drops of buffer solution. This method of inoculation was found to be more accurate and convenient than the use of pipettes.

Time and temperature of incubation: Following inoculation, all tubes are incubated without shaking at 37° C. in an air incubator. Growth usually begins to appear within three or four days as very small flaky deposits on the bottoms of the tubes. When the tubes are shaken, this growth has a characteristic appearance (8, 9, 10) that can be differentiated from almost all types of contamination. A more prolonged period of incubation, however, markedly increases the amount of growth and the ease with which the readings can be made. At the end of fourteen days' incubation the tubes are examined, and the bacteriostatic activity of each compound is recorded as the least amount which completely prevents the growth of the tubercle bacilli. In addition, by a comparison with the amount of growth in the control tubes, partial inhibition of growth can be determined. In the tables in this paper, however, the only concentrations recorded are the smallest which completely inhibit growth of the tubercle bacilli.

The error inherent in this method is a plus or minus one dilution. Experience has shown that the error is frequently much less. As an additional control, however, a series of dilutions of 4,4′-diaminodiphenyl sulfone is included with each set of compounds tested. In all cases the bacteriostatic activity of 4,4′-diaminodiphenyl sulfone varied only between 1.25 and 5.0 mg. per 100 cc. In addition, the *in vitro* tests were performed with all compounds at least twice.

Bacteriostatic tests in the presence of serum and p-aminobenzoic acid: The bacteriostatic action of the majority of the compounds was also tested in the presence of beef serum. These tests were performed by adding aseptically sufficient whole sterile beef serum to the synthetic medium to make a final concentration of 10 per cent. All dilutions were then made aseptically.

When it was desired to test the effect of *p*-aminobenzoic acid on the tuberculostatic activity of other drugs, the PABA was incorporated in the medium in a concentration of 0.1 mg. per 100 cc. Dilutions of the compounds were then prepared as before.

In vivo tests: The methods employed to determine the effect of compounds on experimentally produced murine pulmonary tuberculosis have recently been published in detail (11, 12, 13). Only nine compounds were tested in this manner, and all were administered to the intravenously tubercularized mice by the drug-diet method.

Materials: The chemical compounds used were stock samples except in the following instances: We are indebted to Dr. Henry Gilman, Iowa State College, for compounds Nos. 11, 12, 13, 16, 17, 30, 31, 32, 33, 34, 35, 36, 37, 41, 42, 57, 58, 59, 60, and 61; to Dr. C. S. Marvel, University of Illinois, for Nos. 22 and 44; and to Dr. H. R. Snyder, University of Illinois, for No. 38.

m-and *o*-Toluidine, whose relative activity in our test differs significantly from the results of Bloch *et al.* (1), were converted to acetyl derivatives and identity checked by melting-point comparison.

RESULTS

In vitro Activity in Absence of Serum

Table 1 lists aniline and a series of its simple monosubstituted derivatives with their tuberculostatic activities in simple media. The compounds are arranged, whenever possible, in sets of three, comparing the effect of *ortho*, *meta*, and *para* substitution. In agreement with Bloch *et al.*, the *para* isomers are invariably the most active, frequently causing complete inhibition at dilutions higher than one in five million. These authors found *m*-toluidine (No. 3) inactive and *o*-toluidine (No. 2) slightly active; whereas, from the present measurements *m*-toluidine is intermediate between the *ortho* and *para* isomers and the activity decreases sharply in the following sense: *para* > *meta* > *ortho*. That this is the general pattern of activity with simple *ortho*, *meta*, and *para* isomers is borne out by the results with the chloro, iodo, and pyridyl anilines (compounds Nos. 5 through 13). The last two sets of isomers in table 1 (Nos. 14, 15, 16, and 17) are incomplete, but the isomers available show activity not inconsistent with this trend.

The first six compounds in table 2 show the effect of simple (nonfunctional) polysubstitution on the activity of primary aromatic amines. In the remaining compounds, if the point of attachment of the amino-containing benzene nucleus to other ring systems be compared with simple substitution, e.g., CH_3, et cetera, it is apparent that all the compounds with both *ortho* positions free are very

TABLE 1

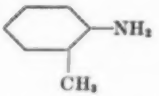
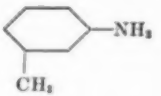
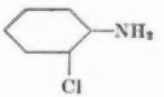
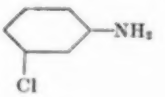
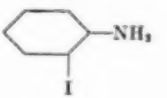
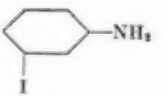
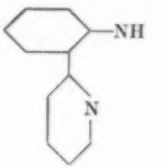
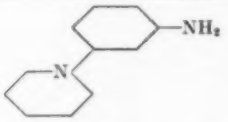
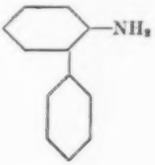
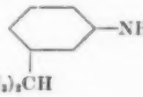
NUMBER	COMPOUND	MOLAR × 10^5	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
1		>110	>10	>10
2		93	10	>10
3		5.8	0.63	10
4		0.73	0.078	>10
5		>78	>10	>10
6		20	2.5	10
7		4.9	0.63	>10
8		>46	>10	>10
9		1.4	0.31	2.5
10*		0.31	0.078	>10
11		29	5.0	>10

TABLE 1—*Continued*

NUMBER	COMPOUND	MOLAR × 10^5	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
12		3.7	0.63	>10
13		0.056	0.095	>10
14		0.92	0.16	>10
15		0.014	0.0024	10
16		0.29	0.039	not done
17		0.14	0.019	not done

* Tested as hydrochloride.

active. Conversely, except for compounds 29 and 35, all compounds with one or both *ortho* positions substituted are distinctly less active than the parent or isomeric compounds (Nos. 18, 20, 21, 22, 23, 25, 31, 32, 39, and 40). The position of No. 33 in this respect is uncertain because the corresponding unbrominated compound was not available for comparison.

While our results parallel those of Bloch *et al.* for α- and β-naphthylamine (compounds Nos. 24 and 25), it is interesting that with the isomeric xylidines (Nos. 18 and 19) the same type of discrepancy appears as with the isomeric toluidines mentioned previously. By the present measurements the compounds with both *ortho* positions free are the more active.

Although Bloch *et al.* gave several examples of inactivating substitution, it is of interest to call attention to these types in particular. The first four compounds in table 3 (Nos. 41, 42, 43, and 44) show the effect of substitution of the amino

TABLE 2

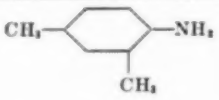
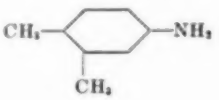
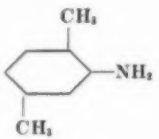
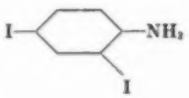
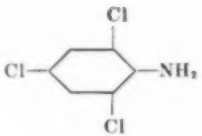
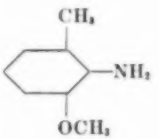
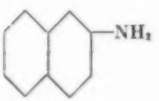
NUMBER	COMPOUND	MOLAR × 10^5	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
18		2.6	0.31	>10
19		1.2	0.16	>10
20*		83	10	>10
21		7.2	2.5	>10
22		>51	>10	>10
23		>73	>10	>10
24		0.13	0.019	5.0
25		1.1	0.16	10

TABLE 2—*Continued*

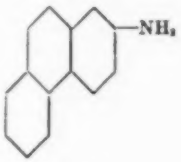
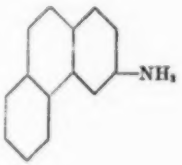
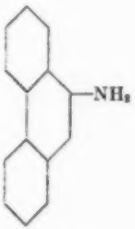
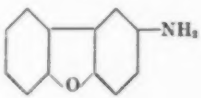
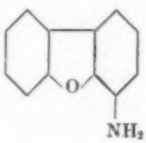
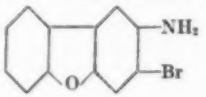
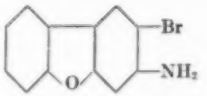
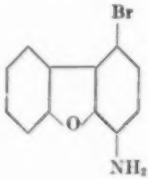
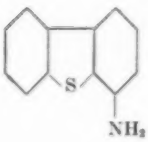
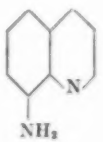
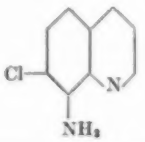
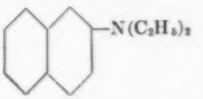
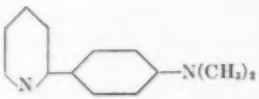
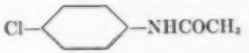
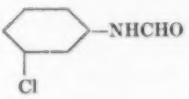
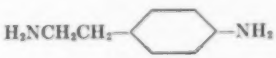
NUMBER	COMPOUND	MOLAR × 10^5	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
26		1.8	0.31	5.0
27*		0.34	0.078	not done
28*		0.17	0.039	5.0
29		1.6	0.31	1.25
30		0.21	0.039	5.0
31*		0.36	0.078	10

TABLE 2—*Concluded*

NUMBER	COMPOUND	MOLAR × 10^6	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
32		>38	>10	>10
33		0.60	0.16	>10
34		1.2	0.31	>10
35		0.20	0.039	10
36		0.20	0.039	5.0
37		0.40	0.078	>10
38		1.1	0.16	>10
39		4.3	0.63	5.0
40		28	5.0	>10

* Tested as hydrochloride.

TABLE 3

NUMBER	COMPOUND	MOLAR × 10^5	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
41		25	5.0	not done
42		25	5.0	not done
43		59	10	10
44		64	10	>10
45		>66	>10	>10
46		>74	>10	>10
47		>73	>10	>10
48		>58	>10	>10
49		>46	>10	>10
50		85	10	>10
51		4.7	0.63	>10
52		18	2.5	>10
53		69	10	>10
54		6.8	1.25	>10

group itself by alkylation and acylation. These changes greatly reduce activity compared with the parent compounds (Nos. 24, 13, 7, 6, respectively) and are reminiscent of the same kind of effect so well known in sulfanilamide derivatives.

Compounds Nos. 45 through 54 show a variety of inactivating effects. Introduction of groups which exist primarily in an ionic form at pH 7, e.g., NH_2 (aliphatic), CO_2H, SO_2H, AsO_3H_2, results in almost entire loss of activity. A similar effect frequently results if the substituent carries a polar group as with Nos. 50, 51, 52, 53, and 54. This behavior bears out the importance of lipophilic character in the substituent group for activity as developed by Bloch *et al.*

It thus appears that with those primary aromatic amines containing only alkyl or halogen substituents the relative activity of the isomers can be predicted with some confidence. Further, a rough estimate of the degree of activity of particular compounds of this class can frequently be made[2].

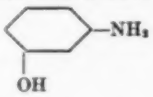
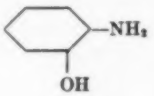
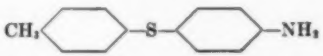
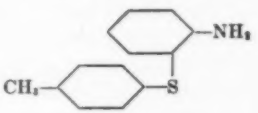
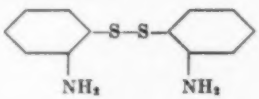
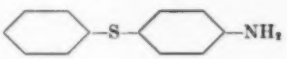
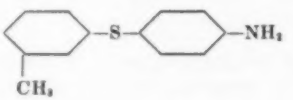
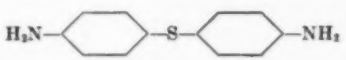
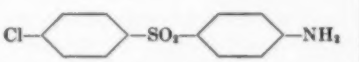
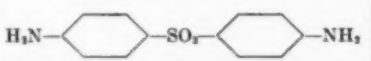
We thus see the emergence of a specificity pattern of activity which would allow the preparation of an endless number of compounds of almost any desired degree of *in vitro* activity within a wide range. This type of correlation is useful in that it simplifies an otherwise bewilderingly complex picture and allows investigation and comparison within this broad class of independent features which bear on their adaptation as chemotherapeutic agents. Some aspects of this latter part of the problem will be dealt with in subsequent papers.

Because of the great complexity of the metabolism of the tubercle bacillus, it would be naive not to expect many exceptions and anomalies to appear in any such correlation. These would be expected to arise with greater frequency as those functional or reactive groups are substituted which bring greater similarity to the usual types of metabolic substances present in cells. Interference with these additional metabolic processes should result frequently in an independent bacteriostatic activity superimposed on the original activity. This points out another, albeit oblique, value of correlations of structure and activity; namely, the identification of new specificity patterns of activity by the appearance of unexpectedly high bacteriostatic values.

In table 4 attention is called to two general types of aniline derivatives which may illustrate the appearance of activity patterns distinct from that shown by the previously discussed simple aromatic amines. Substitution with the hydroxyl group in the *meta* and *para* position is strongly deactivating (Nos. 55, 53, respectively). Number 56, which contains the hydroxyl group in the *ortho* position to the amino group, and which by the general behavior exhibited by other simple aromatic amines should be perhaps the least active, is, however, quite active. This suggests that the bacteriostatic activity of *o*-aminophenol has its origin in a different site or mechanism of action than that of the simple aromatic amines generally.

[2] The possible extension of these generalizations in a limited way to compounds containing heterocyclic amino groups is suggested by the activity of the series of substituted 3-aminopyridines reported by Feinstone (14, 15). The activity grades up with substitution, much as observed by Bloch *et al.* with the purely aromatic amines. It is perhaps no accident in this regard that the three position of the pyridine ring has long been regarded by the organic chemist as an "aromatic" position.

TABLE 4

NUMBER	COMPOUND	MOLAR × 10^4	BACTERIOSTATIC CONCENTRATION	
			Mg. per 100 cc.	Mg. per 100 cc. in presence of 10 per cent serum
55		92	10	>10
56		1.4	0.16	0.31
57		1.5	0.31	10
58		12	2.5	>10
59		1.3	0.31	5.0
60		0.78	0.16	5.0
61		1.5	0.31	10
62		23	5.0	10
63		9.3	2.5	>10
64		10	2.5	5.0

A similar argument can be used to show that the remaining phenyl sulfides and phenyl sulfones in table 4 have bacteriostatic properties as a class which differ from what would be expected if the activity were entirely due to their primary amine content. Compounds 57, 58, and 59 show that *ortho* substitution is not

necessarily deactivating. Introduction of a second amino group *para* in the second ring, as in Nos. 62 and 64 compared to No. 60 and No. 63, results in thirty fold and no deactivation, respectively. This may be contrasted with the greater than five hundred fold inactivation of No. 15 (table 1) by this type of substitution in No. 54 (table 3). The bacteriostatic activity of No. 64, *p*,*p*′-diaminodiphenyl sulfone, is largely nullified by the addition of *p*-aminobenzoic acid while, apparently, the action of the simple primary aromatic amines generally is not affected by this compound. (Compounds Nos. 2, 3, 4, 12, 13, 14, 18, 19, 26, 27, 28, 29, 30, and 37 were tested with added PABA and gave approximately the same bacteriostatic level.) This is added evidence that the bacteriostatic action is qualitatively different with this particular compound and generally validates the possibility that in closely related series new types of activity may be overlooked if attention is directed solely to the similarity in structural and activity features.

In vitro Activity in Presence of Serum

The majority of the compounds of this study were tested *in vitro* in the presence of 10 per cent serum and the results are listed in the last column of the tables. Almost without exception, the activity of the simply substituted amines of tables 1 and 2 is drastically reduced in the presence of serum. The inactivation in frequently ten- to fifty-fold and in some instances is as high as five hundred to one thousand fold. The residual activity in even the best examples is only moderate.

A similar effect with 2-amino-5-butoxypyridine has been reported (16).

It is interesting that compounds Nos. 56, 62, and 64 of table 4 show only two- to four-fold inactivation with serum, confirming that the activity of these compounds may be unrelated to the activity of simple primary aromatic amines generally.

In vivo Results

Table 5 gives the results obtained following the administration of nine compounds by the drug-diet method to intravenously tuberculized mice. With the possible exception of 2-aminodibenzothiophene, none of the compounds exerted a demonstrable suppressive effect on the tuberculous process. This is indicated by the similarity between the average survival times, average weight loss, and the extent and type of the pulmonary lesions as compared with the controls. The possible favorable effect noted with 2-aminodibenzothiophene was indicated only by a predominance of proliferative lesions in those mice treated with 0.05 per cent in the diet as compared with the homologous control group. Even if real, this difference is too slight to be of any practical significance.

The low dosage levels reflect the high degree of toxicity of these compounds. Even with dosages which were nontoxic, as indicated by the survival time, cyanosis was not an uncommon observation with some of the drugs. This was most pronounced with 2-(4′-aminophenyl) pyridine.

This high toxicity taken in conjunction with the pronounced inactivating ef-

TABLE 5

Effect of Compounds on Experimental Mouse Tuberculosis

NUMBER	COMPOUND	AMOUNT IN DIET	NUMBER OF MICE	PER CENT MORTALITY	AVERAGE SURVIVAL TIME	AVERAGE WEIGHT GAIN OR LOSS	AMOUNT GROSS TISSUE CHANGE† LUNGS	PREDOMINANT TYPE OF MICROSCOPIC LESIONS
					Days	*Gm.*		
37	2-Aminodibenzothiophene	0.15% 14 days then 0.075%	10	100.0	16.1	−6.1	2.1+	P
	Controls		8	100.0	19.0	−5.3	4.0+	NE‡
	2-Aminodibenzothiophene	0.05%	10	90.0	24.1	−8.6	3.8+	P
	Controls		10	70.0	25.6	−6.1	3.7+	NE
36	3-Aminodibenzothiophene	0.05%	10	100.0	22.1	−8.2	3.7+	NE
	Controls		9	55.5	25.7	−6.4	3.0+	NE
13	2-(4′-Aminophenyl)-pyridine	0.5% 14 days then 0.25%	10	100.0	13.8	−6.2	2.75+	NE
	Controls		8	100.0	19.0	−5.3	4.0+	NE
	2-(4′-Aminophenyl)-pyridine	0.16% 14 days then 0.08%	9	44.4	26.0	−4.8	3.5+	NE
	Controls		10	70.0	25.6	−6.1	3.7+	NE
30	2-Aminodibenzofuran	0.025%	10	80.0	23.7	−5.7	3.7+	NE
	Controls		9	55.5	25.7	−6.5	3.0+	NE
15*	p-Aminodiphenyl	0.025%	10	60.0	19.5	−3.5	4.0+	NE
	Controls		10	100.0	17.9	−4.9	4.0+	NE
56	o-Aminophenol	0.25%	10	90.0	21.4	−7.7	4.0+	NE
	Controls		10	40.0	24.2	−3.3	3.8+	NE
10	4-Iodoaniline HCl	1.0%	4	75.0	16.0	−3.5	4.0+	NE
		0.5%	4	100.0	23.5	−5.7	4.0+	NE
		0.25%	4	50.0	22.5	+0.2	4.0+	NE
	Controls		4	75.0	24.7	−5.0	4.0+	NE
44	m-Chlorophenyl formamide	0.05%	10	80.0	21.5	−5.7	4.0+	NE
	Controls		10	100.0	17.3	−6.7	3.8+	NE
61	4-Amino-3′-methyldiphenyl sulfide	0.25% 14 days then 0.125%	10	100.0	19.1	−7.4	3.6+	NE
	Controls		8	100.0	19.0	−5.3	4.0+	NE
	4-Amino-3′-methyldiphenyl sulfide	0.083%	10	60.0	25.5	−4.9	3.1+	NE
	Controls		10	70.0	25.6	−6.1	3.7+	NE

* 3-week experiment.

† 1+ = 0 to 10.0% of lungs involved.
2+ = 10.0 to 25.0% of lungs involved.
3+ = 25.0 to 50.0% of lungs involved.
4+ = over 50.0% of lungs involved.

‡ No effect.

fect of serum would seem adequate to account for the failure of these compounds to produce a chemotherapeutic effect. However, the number of examples studied thus far limits seriously the scope of generalization allowable. It would be of

particular interest to investigate representatives of this class of compounds which exhibit outstanding activity in serum, or other evidence of a different mechanism of activity.

SUMMARY AND CONCLUSIONS

This study of a variety of derivatives confirms the prior observation that primary aromatic amines are highly tuberculostatic in simple media.

The activity of aniline derivatives containing an alkyl or halogen substituent markedly decreases, depending on the position of substitution in the sequence *para* > *meta* > *ortho*.

The same trend frequently appears in polycyclic systems, e.g., naphthalene, phenanthrene, if the positions of ring fusion are considered analogous to a point of substitution in aniline.

A consideration of examples of inactivating substitution confirms the importance for activity of lipophilic character in the substituent group.

Limitations of this type of correlation are discussed, and some examples are cited of aromatic amines possessing activity which may not necessarily be related to that of primary aromatic amines generally.

It appears that the generalized tuberculostatic activity of simple primary aromatic amines is drastically reduced, if not obliterated, by the addition of serum.

Nine of these compounds were shown to be without appreciable effect on the course of experimental tuberculosis in mice. The high chronic toxicity of these compounds coupled with their marked inactivation by serum seems adequate to account for the lack of effectiveness *in vivo*.

SUMARIO

Estudios de la Quimioterapia Antituberculosa. I. Las Aminas Aromáticas Primarias Simples in Vitro e in Vivo

Este estudio de una variedad de derivados químicos confirma la observación anterior de que las aminas aromáticas primarias son altamente tuberculostáticas en medios simples.

La actividad de los derivados de la anilina que contienen un alquilo o halógeno como sustituyente disminuye decididamente, conforme a la posición del sustituto en la secuencia *para* > *meta* > *orto*.

La misma tendencia aparece frecuentemente en los sistemas policíclicos (por ej., la naftalina, el fenantreno), si se consideran las posiciones de la fusión anular análogas a un punto de sustitución en la anilina.

La consideración de ejemplos de sustitución inactivante confirma la importancia que posee en cuanto a actividad la naturaleza lipófila del grupo sustituyente.

Discutidas las limitaciones de esta forma de correlación, cítanse algunos ejemplos de aminas aromáticas dotadas de actividad que puede no estar forzosamente relacionada con la de las aminas aromáticas primarias en general.

Parece que la actividad tuberculostática generalizada de las aminas aromáti-

cas primarias simples es reducida radicalmente, sino obliterada, por la adición de suero.

Observóse que nueve de estos compuestos no ejercían efecto apreciable sobre la evolución de la tuberculosis experimental en los ratones. La alta toxicidad crónica de estos compuestos, unida a una inactivación radical por el suero, parece adecuada para explicar esa falta de efecto *in vivo*.

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Case Reports

FATAL ASPHYXIA AS A COMPLICATION OF LUCITE PLOMBAGE[1]

ERVING F. GEEVER AND WILLIAM F. STONE, JR.

(Received for publication June 7, 1949)

In recent years Lucite (methyl methacrylate) has become popular as a nonirritating plastic useful in closing skull defects; also for ocular or dental prostheses and in experimental replacements of segments of large vascular channels like the aorta. More recently, Lucite spheres have been used as a plombage material in extrapleural pneumonolysis in pulmonary tuberculosis. The substance is considered ideal because it evokes little tissue reaction and has little tendency to absorb fluid. Under experimental conditions, the fluid seeping into an extrapleural pocket where the spheres have been introduced for pneumonolysis becomes organized into a permanent fibrous pack or mass. The purpose of this report is to present a case of fatal asphyxia, secondary to erosion of a Lucite sphere into the trachea.

CASE REPORT

This 30-year-old white male entered St. Francis Hospital on February 23, 1949, with a history of severe substernal pain and difficulty in breathing. The patient was seen at home at 3:30 a.m., shortly before entry here. His wife stated that she was awakened by the patient's entering the room and falling across her bed. He was choking, gasping, and holding his chest. His wife called a physician, as well as the fire and police departments for a resuscitator. When the fire department apparatus arrived, artificial respiration was started and maintained. Past history revealed that the patient had contracted pulmonary tuberculosis while a Japanese prisoner-of-war. Artificial pneumothorax was started on the right in 1943 while the patient was still in the prison camp. The disease progressed, however, and at liberation the patient weighed only 80 pounds. Artificial pneumothorax was then started on the left in an Army hospital and continued up to the present time. The right pneumothorax space gradually diminished despite repeated attempts to keep it open and was eventually lost. With re-expansion, a large apical cavity was reopened (figure 1). In October 1947, in a Veterans Hospital, Lucite ball plombage was performed over the right upper chest in an attempt to close the apical cavity. The postoperative course was characterized by suppression of sputum and high fever for four to five days, followed by increase in cough with a large amount of sputum, and then the fever receded. The sputum remained positive for tubercle bacilli up to the present date. For the past eight months the patient had complained of much right upper chest pain and fever between 99° and 100° F. daily. A bronchogram done six weeks before entry revealed that the iodized oil entered the extrapleural space around the Lucite balls (figure 2). He was advised to re-enter the Veterans Hospital to have the balls removed and other treatment instituted. However, he had not yet decided to follow this advice at the time of the present episode.

Physical examination at home and in the hospital showed an unconscious, thin, cyanotic, young adult male with a gasping type of respiration. The pupils were dilated and unresponsive to light. The chest examination revealed breath sounds clearly audible on both sides, but they were coarse and stertorous in character. The heart showed no deviation or displace-

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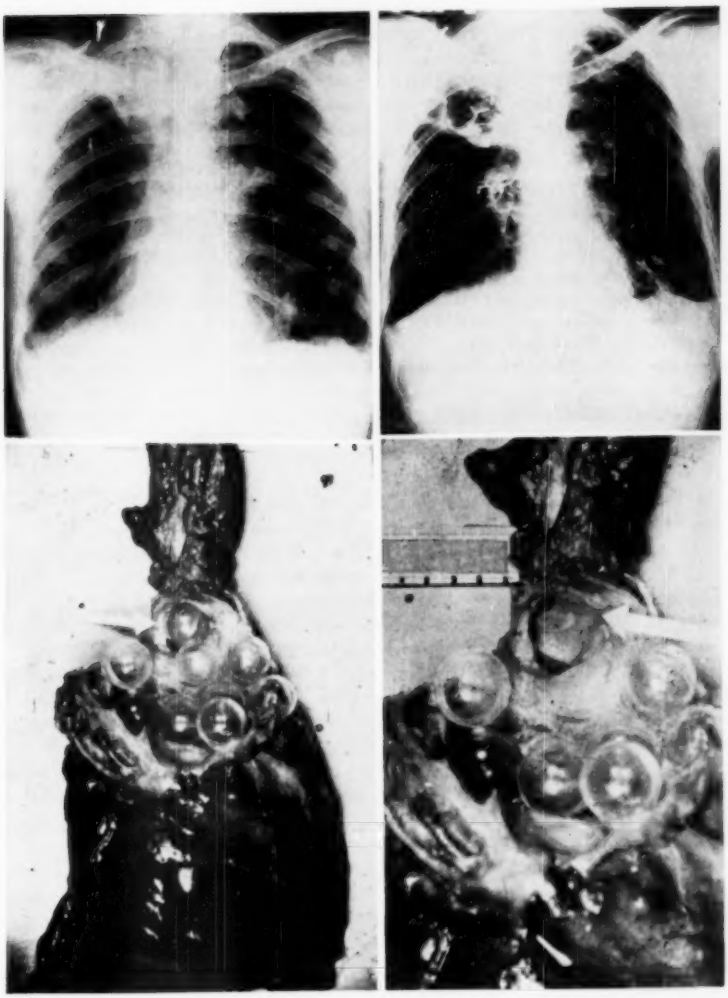

FIG. 1. (Upper left) Roentgenogram of chest showing large apical cavity on the right and artificial pneumothorax on the left.

FIG. 2. (Upper right) Bronchogram demonstrating iodized oil in pocket about Lucite spheres on the right; artificial pneumothorax on the left.

FIG. 3. (Lower left) Larynx, trachea, and right lung photographed from right lateral aspect. Lucite spheres in pocket over apex of lung; arrow indicates sphere eroded through lateral wall of trachea.

FIG. 4. (Lower right) Close-up of eroded zone in lateral wall of trachea.

ment. The heart sounds were weak and rapid. There were no murmurs. Abdominal examination was not remarkable. The clinical impression was pulmonary embolism or thrombosis. The patient was treated by aspiration of air from the left pneumothorax although the pressure in the latter did not appear increased. He was also given demerol intravenously, coramine intramuscularly, and continuous oxygen. There was some temporary response, but relapse occurred shortly thereafter and death resulted at 9:00 a.m., five and one-half hours after entry.

Complete necropsy, including brain examination, was performed. At necropsy the important pathologic changes were in the chest. The right lung weighed 890 Gm. and the upper third was firmly adherent to the chest wall. By sharp dissection a multiloculated, apparently extrapleural pocket was freed. It contained about 100 cc. of caseous yellow fluid and 16 Lucite spheres (figure 3). One sphere had eroded through the right lateral wall of the trachea and was almost completely obstructing the tracheal lumen. The erosion measured 3.0 by 2.5 cm. in surface area, was oval in configuration, and its margins were smooth (figure 4). Microscopically, the margins showed fresh tuberculous granulation tissue. The base of the pocket revealed three openings into the bronchi, two of which were patent. No cavity could be identified in the upper lobe. Scattered caseo-nodose lesions were present in both lungs. A thin-walled bronchiectatic cavity 0.8 cm. in diameter was present in the left upper lobe. The pulmonary arterial circuit was free from emboli or thrombi. The heart showed no evidence of coronary or other disease. Brain examination was negative.

DISCUSSION

The course of pathologic changes in this case seems fairly clear. The extrapleural pocket became infected at some time in the 17 months' postoperative period. The immediate postoperative course was characterized by high fever for four to five days, with little or no sputum. This was followed by increase in cough, diminution in temperature, and expectoration of large amounts of sputum. Infection of the pocket might have occurred at this time. At any rate, the partition between the extrapleural pocket and the large apical cavity disappeared in a process of caseation necrosis. The partition was composed of endothoracic fascia, parietal and visceral pleura, and residual pulmonary parenchyma forming the roof of the apical cavity. Thus the extrapleural pocket became intrapulmonary in position and the bronchi draining the cavity became the proximal portions of multiple broncho-extrapleural fistulae demonstrable by bronchogram. It seems doubtful that the Lucite sphere would have eroded through the tracheal wall if the space had been uninfected. The margins of the eroded tracheal wall were composed of fresh tuberculous granulation tissue and the tuberculous process undoubtedly acted as the spearhead for the penetrating sphere.

Trent, Moody, and Hiatt (1) recently analyzed the results of extrapleural pneumonolysis with Lucite plombage in a series of 51 cases. The follow-up extended over a period of at least one and one-half years to a maximum of two years and ten months. Among the complications they found two in which the balls had dissected caudally and into the mediastinum. Both cases ended fatally. In another case a sphere caused compression of the superior vena cava with engorgement of the neck and arm veins. Their results showed 10 patients improved, 3 stationary, 20 worse, and 18 dead. They believed that the results did not warrant continuation of the procedure.

CONCLUSIONS

A case is reported with erosion of a Lucite sphere into the trachea in a 30-year-old male with pulmonary tuberculosis of six years' duration. The spheres had been introduced in an extrapleural pocket for pneumonolysis and compression of a large apical cavity. The erosion of the trachea resulted in death from asphyxia.

CONCLUSIONES

Asfixia Letal como Complicación del Plumbaje con Lucita

El caso comunicado es de erosión intratraqueal por una esfera de lucita en un varón de 30 años con tuberculosis pulmonar de seis años de duración. Las esferas habían sido introducidas en una bolsa extrapleural para una neumonolisis y compresión de una gran caverna del vértice. Sobrevino la muerte por asfixia.

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PNEUMONECTOMY FOR PULMONARY HEMORRHAGE IN TUBERCULOSIS[1]

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(Received for publication July 29, 1949)

INTRODUCTION

In spite of the relatively high incidence of hemorrhage in tuberculosis of the lung, we have been unable to find a report of pulmonary resection for uncontrollable pulmonary hemorrhage in tuberculosis. The reported incidence of hemorrhage in cases of tuberculosis is relatively high with the over-all incidence of hemoptysis ranging from 20 per cent to 50 per cent of all tuberculosis patients. This is frequently the one symptom which finally causes patients to seek medical care. Profuse hemorrhage, however, occurs in probably less than 2 per cent of the cases.

Resection in tuberculosis in the past few years has been stimulated by the improved therapeutic results, the low mortality, and decreasing complications. The indications for resection are not yet standardized, although classification of indications has been published (1, 2, 3, 4). Maier (1) mentioned recurrent hemorrhage from bronchial lesions and Overholt and Wilson (4) used recurrent hemorrhage following thoracoplasty as an indication. No mention has been made of uncontrollable hemorrhage per se as an indication.

Profuse hemorrhage in pulmonary tuberculosis usually arises from a Rasmussen aneurysm of the pulmonary artery in the region of a cavity incident to the simultaneous extension and healing of that cavity as described by Auerbach (6). With profuse hemorrhage the patient may succumb to the loss of blood, loss of respiratory function because of blood clots in the pulmonary tree, or as an eventual consequence of extensive spread of the bacilli in this ideal vehicle throughout the bronchial tree.

Methods to control hemorrhage are varied but usually include absolute rest and quiet with sedation to control anxiety and excessive coughing. Relaxation of the lung by pneumothorax, pneumoperitoneum, or phrenic crush is indicated. When these methods fail, resection should be considered and used before extensive spread to contralateral lung contraindicates surgery.

REPORT OF CASE

Admission history: A 25-year-old sailor was admitted to the sick-list on January 31, 1948 with a diagnosis of lobar pneumonia because of chills, temperature elevation to 104°F., and a headache. Roentgenographic examination of the chest showed increased density in

[1] The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Bureau of Medicine and Surgery or the Navy Department.

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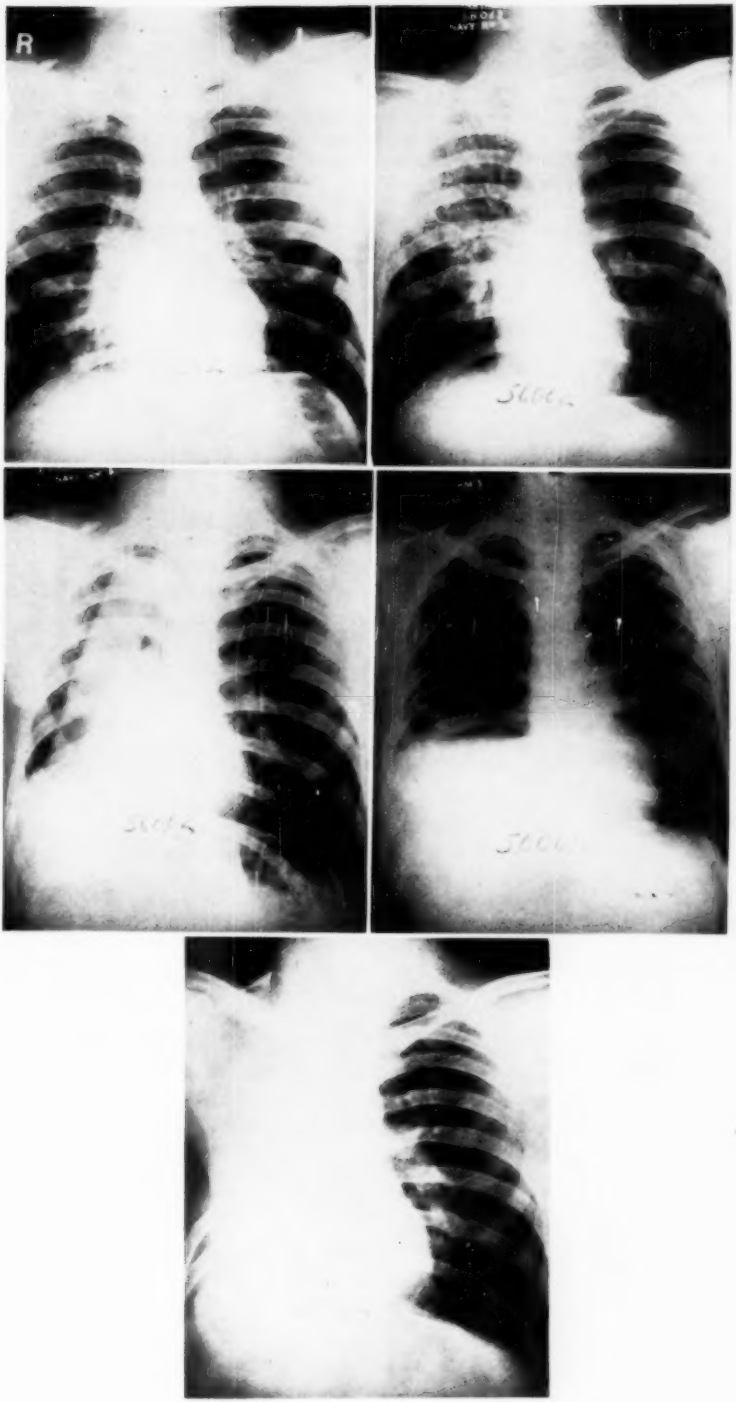
FIG. 1. (Upper left) Roentgenogram, taken just after admission, shows an infiltrate in the right apex with another pneumonic type of infiltrate in the right middle lobe.

FIG. 2. (Upper right) Roentgenogram taken March 6, 1948 shows extension of the lesion in the right upper lobe.

FIG. 3. (Center left) Roentgenogram, taken just after institution of pneumothorax, shows opaque lung on the right.

FIG. 4. (Center right) Postoperative film after right pneumonectomy.

FIG. 5. (Bottom) Roentgenogram taken after thoracoplasty.



Figs .1-5

the right apical area which was suspected to be tuberculosis, while at the right base there was a large area of increased density which was believed to represent nontuberculous pneumonia (figure 1). He had a small amount of purulent sputum which was blood-streaked at times. Smear of this sputum was reported to be four plus for acid-fast bacilli.

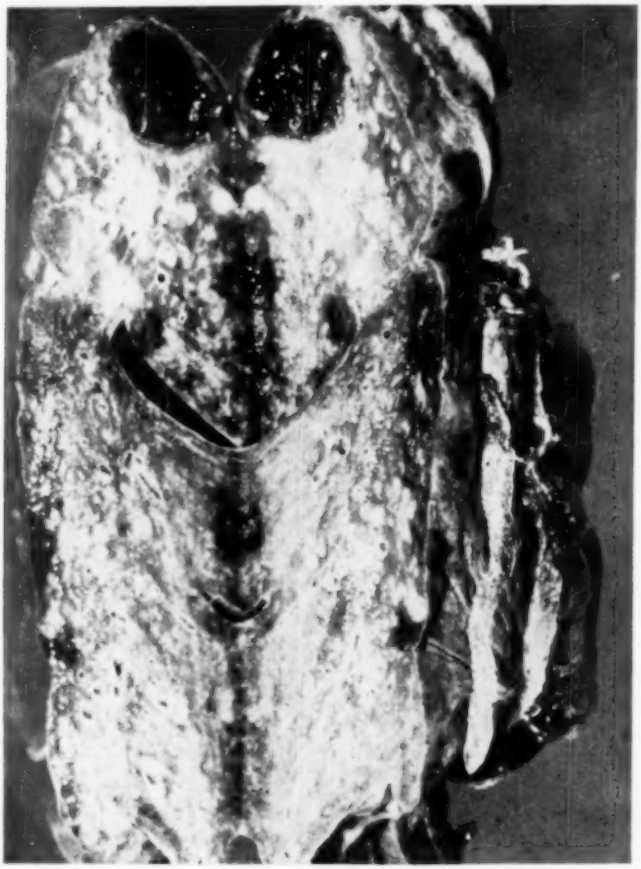


FIG. 6. Photograph of the cut section of the lung shows the large cavity in the apex filled with blood clot. Note the extensive spread of the disease throughout the entire lung.

Past history: The patient admitted that he had had a cough productive of blood streaked sputum in September 1947, but roentgenograms at that time and the routine survey film taken in November of that year were reported as negative. The cough cleared after a short period.

Course: The patient was hospitalized on January 31, 1948 and on February 15 and 16 he expectorated 30 to 90 cc. of blood. His condition rapidly became worse and he lost seventeen

pounds until he was placed on streptomycin therapy. After the start of chemotherapy he began to gain weight again and improved generally, as well as having decreased hemoptysis.

In June 1948 he began to expectorate blood-streaked sputum again and on July 1 an artificial pneumothorax was instituted on the right because of the continued bloody sputum. The lung became opaque and repeated refills were necessary to prevent and treat dyspnea (figure 3). In spite of the pneumothorax, transfusions, and therapy to stimulate coagulation, the patient continued to expectorate up to 720 cc. of blood in a twenty-four-hour period so that resection was advised.

Operation: On July 17, 1948 through a posterolateral incision, a right pneumonectomy was performed. The hilum was exposed directly from behind and the right main stem bronchus was isolated under the arch of the azygos vein and occluded within a few minutes after the chest was entered. The anesthesiologist then aspirated all secretions from the trachea before the vessels were ligated individually in the hilar area.

Postoperative course: The patient had normal convalescence (figure 4). He was given penicillin, 100,000 units twice a day, but was not given streptomycin. On August 30, approximately six weeks after his resection, a right thoracoplasty of ribs two through seven was performed. This was done to prevent mediastinal shift, overdistention of the opposite lung, and to decrease the dead space (figure 5).

Pathology: The entire lung was subcrepitant to noncrepitant and nodular in consistency. A cavity measuring 2.5 cm. in diameter was present in the apex of the upper lobe. The cavity and entire bronchial tree were filled with blood clot (figure 6). Careful removal of clot failed to reveal an aneurysm or a bleeding point. The remaining portions of the lung showed numerous caseous foci. The regional lymph nodes were enlarged and soft but showed no definite caseation.

Microscopic examination showed the large cavity to be old with evidence of activity and it was surrounded by areas of fibrosis. The ages of the tuberculous foci seen throughout the lung varied from the relatively old, with surrounding fibrosis to the newly disseminated spreads.

Follow-up observation: The patient has shown gradual improvement with gain of weight although he has not recovered his normal weight. His cough has decreased to an occasional one with scanty sputum. Studies of sputum or gastric washings have been done in the year following surgery and they have been reported as negative for tubercle bacilli on smear and culture on fifteen occasions. Blood counts and the erythrocyte sedimentation rate are now within normal limits.

SUMMARY

A case of pneumonectomy performed for repeated profuse hemoptysis is reported. When carefully selected, this procedure offers a direct approach to control of otherwise uncontrollable hemorrhage and has the additional advantage of removing the maximum disease foci.

SUMARIO

La Neumonectomía por Hemorragia Pulmonar en la Tuberculosis

Preséntase un caso de neumonectomía ejecutada por hemoptisis profusa repetida. En casos cuidadosamente seleccionados, este procedimiento lleva por vía directa a cohibir una hemorragia que no podría cohibirse de otro modo, a la par que elimina los principales focos patológicos.

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TUBERCULOMA OF THE LUNG, SIMULATING BRONCHOGENIC CARCINOMA[1]

ISIDOR KROSS

(Received for publication July 14, 1949)

Within recent years, as a result of extensive roentgenographic studies among industrial personnel, in the armed forces, and in college students, a considerable number of asymptomatic lung lesions have been discovered. The presence of these abnormalities naturally brings up the question of therapy. The very fact that these abnormal lung shadows are asymptomatic makes the problem much more difficult. Quite obviously, before any form of treatment can be instituted, the diagnosis must be established. When the roentgenographic findings can be definitely interpreted, the problem is quite simple and the appropriate therapy can be applied. There are instances, however, in which the operative findings or the postoperative pathological examination will turn out to be entirely different from the preoperative clinical diagnosis upon which the decision for therapy had been made. Such an instance is the basis for the present report for it is believed that an accumulation and study of such mistaken diagnoses may make for more thorough preoperative study and probably reduce the number of errors.

CASE REPORT

The patient, J. S., was inducted into the United States Navy in 1943 at which time a chest roentgenogram was entirely negative. After serving for three years, he was discharged. At this time he was again examined roentgenographically as part of the routine procedure, and a "homogeneous density about one inch in diameter well circumscribed in the region of the third rib anteriorly" was found. The sputum and the gastric contents were now examined and were found to be negative for tubercle bacilli. Guinea pig inoculation of similar specimens also proved to be negative for tuberculosis. In September 1946 he became a patient at the Mott Haven tuberculosis clinic (New York City Health Department) and roentgenograms (figure 1) taken at this time showed no essential change. Another chest film obtained four months later showed a definite increase in the size of the shadow. Again all examinations for tubercle bacilli proved to be negative. During all this time the patient was entirely asymptomatic. He was transferred to the Montefiore Hospital November 3, 1947. A bronchoscopic examination done by Doctor Arnold at this time revealed that " . . . there was no definite abnormality noted. There was one small mass of mucoid secretion near the carina. This was smeared for tuberculosis cultures and guinea pig inoculations. There was slight thickening of the mucosa in the anterior division of the right upper lobe bronchus." A tuberculin test on November 12, 1947 was faintly positive. When repeated two days later, the tuberculin test was definitely positive. A chest roentgenogram obtained November 22, 1947 was reported: "On the P A tomogram (figure 2) there is a beautiful demonstration of the classic appearance of circumscribed cancer of the anterior axillary segment of the right upper lobe with a sharply rounded mass with lateral streakings representing focal atelectasis with a small central area of necrosis with an irregular lining." The roentgenographic diagnosis also represented the consensus of opinion at the combined medico-surgical conference. Operation was performed on November 24, 1947.

Operation—right pneumonectomy: The preoperative diagnosis was bronchogenic carcinoma of the right upper lobe. A mass, the size of an egg, was present in the right upper lobe. The mass reached the anterior surface of the lung and at this point appeared as a de-

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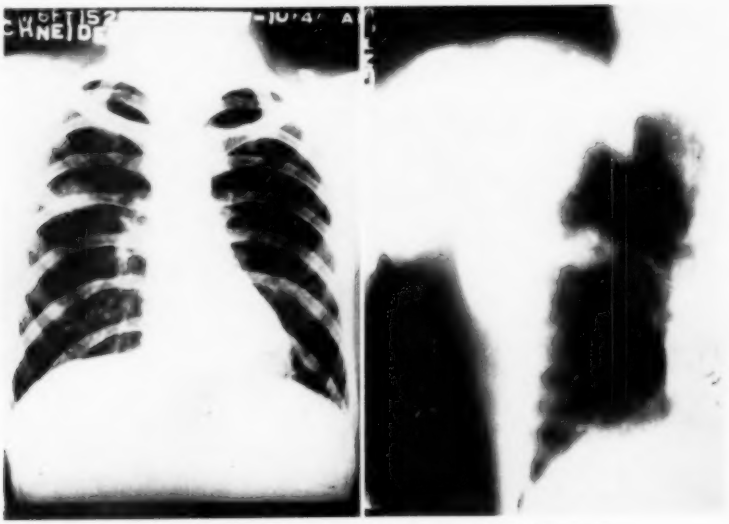

FIG. 1. (Left) Roentgenogram showing tumor in second right interspace.
FIG. 2. (Right) Tomogram showing central area of necrosis.

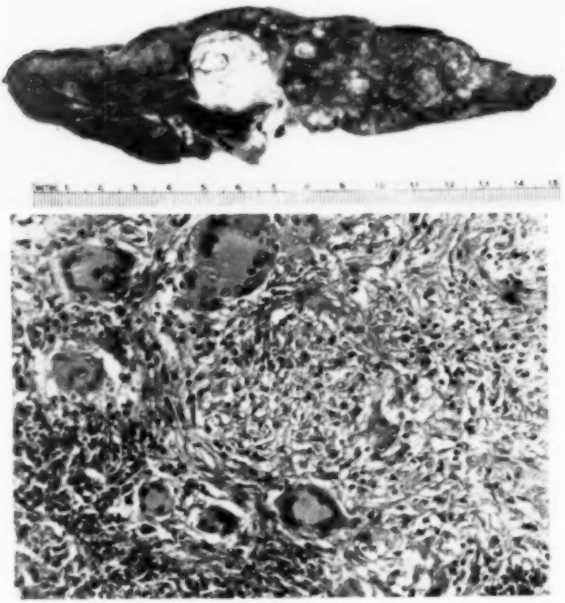

FIG. 3. (Top) Longitudinal section through formalinized lung.
FIG. 4. (Bottom) Section taken from the periphery of the tuberculoma showing a typical tubercle. High power magnification.

pressed, grayish substance, hard to the touch. The free anterior border of the right upper lobe was adherent to the mediastinal pleura just above the level of the hilar structures. An incision was made three inches above the level of the angle of the scapula, beginning about two inches from the mid-line posteriorly and continuing downward and outward beneath the angle of the scapula and forward over the sixth rib to the mid-clavicular line. The sixth rib was excised subperiosteally throughout its entire length and the pleural cavity was opened through the periosteal bed. The phrenic nerve was crushed and the medisatinal pleura was incised laterally to the nerve. The hilar structures were exposed and the vessels were ligated individually. The right main bronchus was closed with a layer of mattress sutures approximating the anterior and posterior walls. The free edges were united with interrupted sutures. The stumps of the hilar structures were covered with a layer of mediastinal pleura. The chest wall was closed in anatomical layers without drainage.

Pathological report. Gross description (Doctor Berkman)

The specimen consisted of a collapsed, shrunken, flattened, partially dried-up lung which was incompletely fixed in insufficient formalin (figure 3). An irregular, opaque, gray, slightly depressed area of thickening, measuring 3.0 cm. in length and up to 0.5 cm. in width, ran parallel to the horizontal fissure and was roughly at the base of the line of division of the anterior and posterior bronchopulmonary segments of the right upper lobe. Just beneath the scar, there was a firm, smooth, sharply circumscribed rounded mass of golf-ball size. Irregular small groups of nodules were palpable just beneath the pleura on the inferior surface of the lower lobe, in the posterior inferior margin of the upper lobe, and medially at the base of the upper lobe. There were scattered patches of atelectasis in the medial aspects of the upper lobe and the middle lobe. The mass consisted of cheesy, greenish, friable necrotic material surrounded by a gray translucent capsule 0.3 cm. thick. It was covered by a thin rim of compressed lung tissue, within which a few scattered encapsulated caseous foci up to 1.0 cm. in size were present. These extended to the pleura. The remaining palpable nodules consisted of small clusters of poorly to sharply circumscribed, encapsulated to nonencapsulated, firm to friable, caseous areas varying in size from a few millimeters to one centimeter. The mucosal surface of the bronchi was smooth except for one centimeter in the main bronchus to the upper lobe. At this point, two centimeters from its origin, the mucosa was thickened postero-inferiorly and granular just proximal to the subdivision of the bronchus into its apical posterior and anterior branches. This probably corresponded to the site of the previous bronchoscopic biopsy. No bronchial communication with the mass in the upper lobe could be demonstrated. The hilar lymph nodes were firm and deeply anthracotic. Section revealed scattered, gray, pinhead- to pinpoint-sized spots, but no area of frank caseation or calcification. Direct smear of the caseous material in the large upper lobe lesion revealed numerous acid-fast organisms.

Microscopic description: The large tuberculoma at the base of the upper lobe was, in part, well encapsulated by a thick layer of dense collagenous and hyalinized connective tissue (figure 4). Elsewhere, however, only thin zones of vascular tuberculous granulation tissue intervened between it and the surrounding lung tissue. The latter was seeded with caseating single and conglomerate tubercles. There was a variable amount of compression with distortion of alveoli and fibrosis of their septa, and complete replacement fibrosis in the vicinity of the pleural scar. Within the caseous necrotic center of the large tuberculoma, shadowy outlines of pulmonary parenchyma persisted. Elsewhere no architecture could be made out. Scattered cholesterol spaces, much nuclear dust, and a few small calcific deposits were present. Sections at the various points of dissemination, noted grossly, revealed numerous single and conglomerate tubercles, usually with caseation and with surrounding zones of tuberculous granulation tissue of varying thickness. In one section a caseating lesion had ruptured into the lumen of a small bronchiole. The hilar lymph nodes contained epithelioid and giant cell tubercles. The bronchus to the right upper lobe was edematous, congested, and diffusely infiltrated by lymphocytes and plasma cells. The basement mem-

brane was thickened and the underlying lung tissue studded with tubercles, but the bronchus proper was free of tuberculosis at this level.

Diagnosis: Disseminated tuberculosis of right lung and hilar lymph nodes with large tuberculoma at base of right upper lobe.

COMMENT

From a practical point of view, it is obvious that treatment had to be determined solely on the interpretation of the roentgenogram since the patient was entirely asymptomatic and the physical examination was negative. The consensus of opinion of all who had examined the patient and who had seen the early roentgenograms was that he had a tuberculoma in spite of the complete absence of any positive evidence of tuberculosis. This was explained on the assumption that the lesion was the end result of a healed tuberculous focus. When subsequent serial roentgenograms showed a definite increase in the size of the shadow, however, the diagnosis of a healed calcified focus came to be doubted. The doubt became more marked when the patient remained completely free from any disturbances that could be associated with a spreading active tuberculous infection such as cough, expectoration, fever, or toxicity. Under these circumstances, the diagnosis and subsequent treatment had to be determined entirely by the interpretation of the films. It is interesting therefore to note that the attending physician was fairly unequivocal in his interpretation and reported that the tomograms showed all the characteristics of a definite, classic picture of a cancer. It is also significant that this same opinion was shared by the other staff members whose experience in roentgenographic interpretation was extensive and thorough. That such errors are not uncommon can be seen even by a cursory review of the recent literature. Friedlander and Wolpaw (1) report 4 cases of carcinoma of the lung which at operation were found to be chronic inflammatory lesions, and even after inspection at operation were still considered to be carcinoma. Graham and Singer (2) report 3 cases in which operation was performed (with a preoperative diagnosis of carcinoma) where the lesion proved to be chronic inflammation. Gottlieb (3) has recently reported a series of cases in which instances of atypical pneumonia, lung abscess, Loeffler's syndrome, and similar conditions simulated the appearance of bronchogenic carcinoma. Kissin and Cohen (4) report an interesting case in which a large healed tuberculous focus was diagnosed as a neoplasm of the lung. At autopsy the true nature of the lesion was made clear. That the reverse situation occurs is seen in a report of Siltzbach (5) in which 2 patients with proved carcinoma of the lung had been diagnosed and treated for tuberculosis for a considerable period of time. In a discussion of the differential diagnosis of pulmonary lesions, Thornton, Adams, and Bloch call attention to the fact that calcification never occurs in malignant tumors and is therefore strongly indicative of tuberculosis. Haight and Farris (7), however, make the contrary statement that "a wide variety of intrathoracic lesions may contain calcium salts which are deposited as elsewhere in the body according to the universal principle that necrotic tissues which cannot be absorbed will become impregnated with calcium salts."

When the subject of treatment comes up, we are again confronted by a problem. Is a tuberculoma the end product of a healed and therefore an innocuous tuberculous lesion, or shall it be considered to be still active and hence a focus for spreading infection? Here again we have conflicting evidence. According to Griffith (8) "the life of tubercle bacilli in a retrogressive lesion may be relatively brief and old encapsulated lesions rarely, if ever, contain living tuberle bacilli." Feldman and Baggenstoss (9) also found "that the lesions of the primary complex of tuberculosis, when definitely encapsulated and sclerotic, seldom contain viable or virulent bacilli." They examined, for the most part,

caseous Ghon tubercles or lymph nodes obtained at autopsy from unembalmed bodies of persons who died from causes other than tuberculosis. Emulsions from individual lesions, 123 in number, were studied. Each emulsion was used to inject two guinea pigs and for the preparation of eight cultures. They could demonstrate tuberculosis in only one lesion. In contrast to these findings, however, is the report of Jacobeus (10) of a patient in whom a tuberculoma was diagnosed as a pulmonary neoplasm. This patient was operated upon and tubercle bacilli were obtained from the lesion. The patient developed a tuberculous infection of his wound and died. At autopsy, a tuberculous pleurisy and miliary tuberculosis were found. Evers *et al.* (11) report an interesting case of a patient in whom a pulmonary shadow was found accidently on routine roentgenographic examination. Except for the shadow in the lung, the examination was entirely negative, and subjectively the patient was asymtomatic. Repeated monthly roentgenograms showed no change in the appearance of the density. The skin reaction to tuberculin was positive. All other tests for tuberculosis were negative. A lung puncture was made and a guinea pig was inoculated with the material obtained which was thus proved to contain tubercle bacilli. About ten weeks after the lung puncture, the patient suddenly developed cough, expectoration, and dyspnea, and the sputum became positive for tubercle bacilli. In the absence of an infiltrating lesion (as judged by the films) the authors came to the conclusion that the pulmonary lesion had a direct bronchial communication and that there was imminent danger of a bronchial spread. On that basis they decided to do a prophylactic pneumonectomy which was performed in two stages. A tuberculoma of the left upper lobe was found which contained liquid material enclosed in a capsule about three millimeters thick. The patient made an uneventful postoperative recover. These cases are similar to the one of the present report in which there is an apparently healed or inactive lesion, but in which subsequent events prove the lesion to be quite otherwise. The only conclusion to be drawn is that at the present time no general rules for diagnosis and treatment can be made and that each case, after thorough and detailed study, must be treated individually on its own findings.

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AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

Report of Clinical Subcommittee

CURRENT STATUS OF DRUG THERAPY IN TUBERCULOSIS

Committee on Medical Research and Therapy

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INTRODUCTION

The introduction of several additional agents into the drug therapy of tuberculosis has increased the need for perspective in the consideration of the proper role of such drug therapy in the over-all treatment of tuberculosis. Whereas additional information obtained since the Committee reported on streptomycin and dihydrostreptomycin in the treatment of tuberculosis[1] has made it possible to employ these agents with more precision than previously, much remains to be determined as to the best manner of their application, and further extensive and careful investigation is needed before they may be introduced freely into general use.

In many tuberculous conditions there is as yet no evidence that various drugs with antituberculous properties lead to late results superior to those obtained by such established forms of therapy as bed rest and collapse therapy, although the use of the drugs appears to be associated with perhaps temporary favorable changes more promptly and more uniformly. The effect of drug therapy upon the immune forces of the host is not known. The exact effect of such drugs on tuberculous lesions in different stages of the inflammatory process is not known. Two deterrents to the use of any antituberculous drug are recognized: toxicity, and the emergence of drug-resistant strains of tubercle bacilli. The exact significance of laboratory determinations of bacterial resistance has not as yet been determined through accurate clinical evaluation.

For these reasons the Committee believes that in general it is desirable to withhold drug therapy if other satisfactory therapy for a tuberculous condition is available, and looks with disfavor on the practice of utilizing drug therapy prior to institutional care or as an alternative to adequate bed rest, collapse therapy, or other surgical treatment, in the hope that such procedures may be avoided.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

Streptomycin or its derivative, dihydrostreptomycin, remains the drug of first choice in the treatment of various forms of tuberculosis. The present recommendations of this Committee are made in the light of additional information obtained since the previous report was published.[1]

Further evaluation has demonstrated that for adults one gram of streptomycin ad-

[1] Report of the Clinical Subcommittee: Streptomycin in the Treatment of Tuberculosis, Am. Rev. Tubere., 1949, *59*, 106.

ministered in a single dose intramuscularly, or one or two grams of dihydrostreptomycin in one or two injections, is the best compromise between the greater toxicity of higher daily dosages and the lessened therapeutic efficacy of smaller daily dosages for all tuberculous conditions except miliary tuberculosis and tuberculous meningitis. It is sometimes preferable to compute the daily dose of streptomycin[1] for adnlts on the basis of 20 mg. per Kg. of body weight (the approximate equivalent of one gram per day) or 40 mg. per Kg. of body weight (the approximate equivalent of two grams per day). In miliary tuberculosis and tuberculous meningitis in adults, two or three grams a day, given intramuscularly in two or three doses of one gram each, are believed to be desirable.[2]

It has been demonstrated that the rate of emergence of streptomycin-resistant tubercle bacilli can be reduced in two ways: (*1*) by administering streptomycin at greater intervals, as one gram every third day or twice a week; and (*2*) by combining the daily administration of streptomycin with the daily administration of para-aminosalicylic acid (see below). The combined therapy, however, has been found to have the greater effect on the delay of the emergence of streptomycin-resistant strains of tubercle bacilli, and has also been found to be more effective therapeutically.

The optimal duration of a course of streptomycin therapy, whether administered alone or in combination with para-aminosalicylic acid, has been less precisely determined. Streptomycin administered alone for as long as 90 or 120 days results in the emergence of tubercle bacilli resistant to streptomycin in a high percentage of patients, denying to such patients the value of re-treatment with the drug in case of need. Administration for 42 days or less, on the other hand, apparently has resulted in less satisfactory therapeutic effects. The Committee recommends, therefore, in general, the duration of daily streptomycin administration without para-aminosalicylic acid be in the range of 42 to 60 days. When streptomycin and para-aminosalicylic acid are administered in combination, the duration may with reasonable safety be in the 90- to 120-day range. Present evidence indicates, however, that combined therapy of such duration will merely reduce the incidence of streptomycin resistance (as compared to that observed when streptomycin alone is used for a comparable period of time), not that it will prevent its occurrence in all

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[1] In this section further reference to streptomycin will be understood also to refer to its hydrogenated derivative, dihydrostreptomycin.

[2] Children often require relatively higher doses of streptomycin than adults, more than 20 mg. per Kg. often being given. In one large clinic the following schedule has been employed safely and effectively:

Weight of child	*Gm. per day*
Under 10 pounds	0.30
10 to 19 pounds	0.40
20 to 39 pounds	0.50
40 to 59 pounds	0.60
60 to 89 pounds	0.75
90 pounds or over	1.00

As in adults, children with miliary tuberculosis and tuberculous meningitis apparently require larger doses than in other forms of tuberculosis, and it has been demonstrated that a very small infant may safely receive 1.0 Gm. of streptomycin intramuscularly daily. In tuberculous meningitis in adults, intrathecal administration of streptomycin should approximate 50 mg. two or three times a week, for the first two or three months of therapy. In children 50 mg., or even 100 mg., per injection may be given intrathecally. Superior results in the treatment of tuberculous meningitis in children are believed to have been obtained by combining streptomycin with other drugs with antituberculous properties, such as Promin or Promizole.

instances. Individualization of the drug therapy of tuberculosis is desirable and even essential, both according to the tuberculous condition to be treated and according to the severity of the individual case.

For tuberculous meningitis and acute hematogenous (miliary) tuberculosis, streptomycin therapy of considerable duration, preferably in combination with other antituberculous agents, is recommended. When streptomycin is indicated for tuberculous lesions of mucous membranes, tuberculous sinuses and fistulae, tuberculosis of the peritoneum and pericardium, and acute tuberculous lymphadenitis, streptomycin alone or in combination with para-aminosalicylic acid may be used, and courses of relatively short duration are generally satisfactory. Streptomycin and para-aminosalicylic acid administered as combined therapy of 90 to 120 days' duration appear to be the drug treatment of choice in the acute and progressive forms of pulmonary tuberculosis, tuberculosis of the genitourinary tract and of bones and joints. In these conditions, however, such therapy will be employed often in conjunction with other indicated therapy, especially surgery (and other forms of collapse therapy or immobilization), and it is important to exercise discriminating judgment in the timing of the use of the drug as an adjunct to such other procedures.

By reducing the incidence, or delaying the emergence, of streptomycin resistance, combined therapy with streptomycin and PAS shows promise of decreasing to a significant degree the sharp therapeutic limitations which exist when streptomycin alone is employed. It should be emphasized, however, that the problem of streptomycin resistance has by no means been eliminated. Hence careful integration of streptomycin with other forms of therapy, and careful planning of the over-all therapeutic attack, continue to be matters of great importance if optimum results are to be achieved. This principle applies in general to all forms of tuberculosis in which drug therapy is indicated. Special note should be made of its importance when streptomycin either alone or in combination with other drugs is employed in the treatment of those forms of tuberculosis in which collapse therapy or excisional surgery is also indicated. Employment of streptomycin in courses of three weeks' duration (one week before and two weeks after) with single-stage surgical procedures has been found to reduce various tuberculous operative complications, but best results have been obtained by a careful integration of thoracic surgical procedures with longer courses of drug therapy where such are indicated and where such integration is possible. It is not considered advisable to employ streptomycin as a routine prophylactic for each stage in multiple-stage operations for tuberculosis.

DIHYDROSTREPTOMYCIN

On the basis of the information available at present, dihydrostreptomycin has been found to show no advantage over streptomycin with regard to therapeutic efficacy, nor is it established that dihydrostreptomycin is as effective as streptomycin. There has been no change in the rate of emergence of resistant organisms with the use of dihydrostreptomycin.

The over-all incidence of vestibular disturbance, as shown by the presence of vertigo or ataxia, and reduced response to caloric stimulation has been found to be less with dihydrostreptomycin than with streptomycin. This is the case when identical dosage regimens of the two drugs are compared, and may also be true if doses of dihydrostreptomycin larger than those of streptomycin are employed. The evidence with respect to the incidence of deafness after administration of streptomycin and dihydrostreptomycin is more controversial. Whereas some reports suggest that there is slightly greater incidence of deafness associated with dihydrostreptomycin therapy than with streptomycin therapy, when identical regimens of treatment are used, other reports present convincing evidence that

the auditory toxicity of dihydrostreptomycin is not greater than that of streptomycin, and may be less. In neither case is deafness of great clinical importance likely to occur in the doses ordinarily employed (one to two grams a day).

PARA-AMINOSALICYLIC ACID

Para-aminosalicylic acid (PAS) as an antituberculosis agent was first introduced by Lehmann in 1945. Studies have revealed that PAS does exert a definite bacteriostatic effect on the tubercle bacillus, both in the test tube and in the animal body, and that it is well tolerated in therapeutically effective doses. PAS is effective in treating established tuberculosis in guinea pigs, for example, but it is less effective than streptomycin.

Para-aminosalicylic acid is relatively nontoxic, although it has been reported by Lehmann to tend to produce hemorrhage in high blood level concentrations. It may be toxic to the liver in some patients, but this question must be investigated further. When given orally it may produce symptoms of gastrointestinal irritation in a high percentage of patients. In order to minimize these symptoms it is suggested that PAS be administered as the sodium salt in an aqueous solution.[4] At present a dosage of three grams four times a day with meals (a total of 12 grams daily) appears to be adequate and to be well tolerated by most patients. When a patient cannot tolerate this amount of PAS without excessive symptoms, reduction of the daily dose to 10 grams or even less may be necessary. There appears to be no advantage in using PAS tablets whether enteric-coated or not unless it be a matter of convenience in administration. Other toxic manifestations such as hypersensitivity phenomena and liver damage are best handled by stopping the drug. Parenteral administration is possible but not advisable except in extreme emergencies.

Para-aminosalicylic acid given alone in the treatment of tuberculosis has limited therapeutic benefit compared with streptomycin, and furthermore may result in the emergence of bacillary resistance to PAS when administration is prolonged. At present the principal indication for the use of PAS alone is for the patient in whom bacterial resistance to streptomycin has already occurred. By far the most effective use of PAS in other patients is in combination with streptomycin.

In summary, the advantages of combined therapy appear at the present time to be: (*1*) greater therapeutic effectiveness than can be obtained with either streptomycin or PAS alone; and (*2*) postponement of the emergence of streptomycin-resistant strains of tubercle bacilli in treated patients. In the light of present evidence it appears justifiable to conclude, therefore, that in patients for whom drug therapy is indicated and whose organisms are not resistant to streptomycin, combined administration of streptomycin and PAS is usually the drug therapy of choice.

THIOSEMICARBAZONES

The Clinical Subcommittee has received with great interest and appreciation the report of Dr. H. Corwin Hinshaw and Dr. Walsh McDermott on the study made in Germany by them on the use of the thiosemicarbazone "Conteben" (TB1/698)[5] in the treatment of tuberculosis.

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[4] The following preparation is suggested: add 60 Gm. of $NaHCO_3$, and then 100 Gm. of PAS to sufficient water to make a total volume of 500 ml., in a vessel sufficiently large to permit effervescence. Five ml. of the resulting solution will contain 1.0 Gm. of PAS. Since there is rapid deterioration in such solution, it should be kept refrigerated and not used more than 48 hours after preparation. Flavoring may be useful.

[5] Am. Rev. Tuberc., January 1950, *61*, 145.

Proposed proprietary names in the United States: "Tibione" (Schenley Laboratories, Inc.) and Myvizone (E. R. Squibb and Sons).

The Subcommittee proposes to encourage additional studies of this substance, especially more extensive research in the bacteriological, pharmacological, physiological, chemical, toxicological, and clinical aspects of the uses of this compound in the treatment of tuberculosis. It would seem best to utilize the facilities of organized groups of investigators functioning well in allied research, namely, the United States Food and Drug Administration, the Public Health Service, the medical departments of the Veterans Administration, the Army, and the Navy, and public and private institutions and workers supported by various grants and aids.

It is the judgment of the Subcommittee that further research along the lines indicated will determine whether the thiosemicarbazones will be used best in the treatment of tuberculosis as primary drug therapy, or as adjuncts to other drugs. It is not believed that TB1 should be employed generally in the treatment of tuberculosis until more definite information is available concerning its limitations and potentialities.

OTHER DRUGS

As would be anticipated from studies in the laboratory, aureomycin has been found to be entirely ineffective in the treatment of tuberculosis in a series of patients suffering from various forms of the disease. Sufficient information is not available as to the effect of chloramphenicol on tuberculosis to permit a statement at this time. Present studies indicate that neomycin, while active against the tubercle bacillus *in vitro*, and *in vivo* in animals, is as yet too toxic to be of value in the treatment of human tuberculosis. Unless toxicity can be reduced by further purification, or by chemical alterations in the structure of the drug, use of neomycin for the treatment of patients cannot be recommended at present, even on an experimental basis.

Letters to the Editors

CONTAGIOUSNESS OF COCCIDIOIDOMYCOSIS

To the Editors of The American Review of Tuberculosis:

In the January 1950 issue of The American Review of Tuberculosis there are two articles on the subject of coccidioidomycosis, with particular reference to pulmonary coccidioidomycosis. The authors of the articles believe that their studies, consisting of experiments with guinea pigs, strongly indicate that "coccidioidomycosis can be contagious, and until proved otherwise should be considered so."

That coccidioidomycosis is noncontagious from man to man has long been believed. A study by associates and myself (Bass, Schomer, and Berke: Am. Rev. Tuberc., 1949, *59*, 632) of intimate family contacts of army veterans with residual cavitary coccidioidal lesions has added further evidence of noncontagiousness.

The significance of this difference of opinion is greater than mere academic controversy. It is of vital importance to the patient and his family to know that isolation (such as is indicated in tuberculosis) is unnecessary. In fact, since the patient with residual lesions, including cavities, generally has few, if any, symptoms and is well able to engage in gainful employment, the entire matter of socioeconomic adjustment becomes dependent on the question of infectivity of his disease.

It is not intended here to make a critical analysis of the two articles emphasizing the contagiousness of coccidioidomycosis. However, regardless of the value of the experiments insofar as they lend themselves to conclusions, the possible pitfalls of correlating the results of animal experimentation with humans must be mentioned. The statement that the high incidence of infection of the permanent population of the southern San Joaquin valley of California "may speak as well for the disease being contagious as for the theory that only the chlamydospores of the vegetative phase disseminated by dust can infect man" is perhaps best answered by a few questions. Why are there no cases of coccidioidomycosis except among those who are exposed to the dust in the endemic areas? Why have the army veterans that we have studied, after leaving the southwest desert, not transmitted the disease to other military personnel with whom they have come in close contact? Why have the intimate family contacts of New York City veterans with cavitary coccidioidomycosis not become infected?

In the light of all the evidence so far established, and particularly from the standpoint of the welfare of the patient as well as the extent of the public health aspects involved, it would appear correct to say that coccidioidomycosis in man should be considered noncontagious until definitely proved otherwise.

Very truly yours,

RUDOLPH BERKE

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January 20, 1950

THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION

To the Editors of The American Review of Tuberculosis:

We have read Dr. A. Henderson's comments in the December, 1949 issue of the American Review of Tuberculosis on our article "The Effect of Antihistamine Medication on the Tuberculin Reaction in Children" which appeared in the September, 1949 edition of the American Review of Tuberculosis. To avoid misunderstanding and confusion in the minds of the readers, we feel that an answer is indicated.

His first criticism is that we have incorrectly inferred that a relationship exists between skin reactions due to histamine and other allergens like ragweed, timothy, et cetera, and the skin reaction is an individual hypersensitive to tuberculin.

1. If he read our paper carefully, he would have noticed that we only mentioned the two types of reactions to show their dissimilarity and in no way inferred that they were similar. In fact, our very findings that antihistamine medication has no effect on the tuberculin reaction further emphasizes this dissimilarity and corroborates the work of Zinsser and others that in the tuberculin skin reaction histamine liberation plays an unimportant part.

2. He further states that we used homeopathic doses and used them for only four days. He apparently forgets that we were dealing with children from five to eleven years and we used doses which in our experience and in that of others gave excellent clinical results in allergic states such as urticaria and allergic rhinitis. Furthermore, we purposely used the smallest effective dose at first in order to compare it with the results obtained in ten children where we used much larger doses. The dose of 240 mg. of pyribenzamine daily on the ten children, considering their age and weight, is much larger than the maximum dose of 500 mg. per day on an adult (the maximum dose referred to by Dr. Henderson).

3. Another criticism is that we used the antihistamine for too short a time, for four days, and he cites his results where he attained a temporary reversal of the tuberculin after he used large doses of antihistamine for six months. It is common knowledge that when an antihistamine drug is effective in most allergic states it shows results in a matter of minutes and hours, but not months. The tuberculin reaction, as is well known, can be temporarily diminished or entirely suppressed by some unknown factors which appear in quite a number of conditions like measles, scarlet fever, mumps, pertussis, miliary tuberculosis, and in starvation and low-protein diets. It is quite possible that the results reported by Doctor Henderson after using a potent drug for six months was caused by some factor or factors other than antihistamines.

4. Our findings, furthermore, have recently been corroborated by two papers which appeared subsequent to the submission of our article for publication. One paper by Leo H. Criep and associates appeared in the June, 1949 issue of The American Review of Tuberculosis. They found no effect of pyribenzamine on the tuberculin reaction even when the same antihistamine was given intradermally and the tuberculin was injected over the same site a few hours later.

Similarly, Edwin L. Kendig, Jr., *et al.* in the December, 1949 issue of the Journal of Pediatrics reported that the administration of antihistamine and pyribenzamine by mouth produced no change in the skin reaction of the tuberculin patch test.

We wish to thank Doctor Henderson for his comment and criticism, but fail to see how any of the factors he mentioned has succeeded in rendering the results of our study delusive.

ELI FRIEDMAN
IRVING SILVERMAN

January 20, 1950

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

Edited by LAWRENCE B. HOBSON

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CLINICAL STUDIES, TUBERCULOSIS

Tuberculosis of Cervical Nodes and Tonsils.—During the war in Finland (1941–1944) the tonsils from 30 soldiers with clinically diagnosed cervical lymph node tuberculosis were examined for the presence of tuberculous infection. In this group about 50 per cent gave a history of previous tuberculosis and 80 per cent showed evidence of pulmonary lesions, none of which were active at the time of observation. The tonsils removed in each case were divided, one-half being digested, concentrated, and injected into a guinea pig and the remaining half serially sectioned and examined microscopically. Only one pair of tonsils was found to be infected. In this case, extensive guinea pig tuberculosis followed inoculation with the concentrate, and typical lesions were observed in the stained sections of tonsil. It was concluded that the single case of tonsillar tuberculosis observed was probably secondary to demonstrated pulmonary disease; cervical lymph node tuberculosis in adults, at least, is most frequently secondary and hematogenous. Primary tonsillar tuberculosis appears to be rather rare.—*Cervical lymph node tuberculosis and the tonsils, M. Pentti, Acta path. et microbiol. Scandinav., 1949, 26: 603.*—*(V. Knight)*

Tuberculous Mediastinal Adenopathy.—Tuberculous mediastinal adenopathy was studied in 22 young inductees in the French Occupation Army during 1945–1946. Of the 22 patients, 15 came from rural areas. The diagnosis of primary tuberculosis could not often be based on the demonstration of tuberculin conversion because of the absence of previous tuberculin tests. All cases were considered typical of primary tuberculosis, however, because of clinical and roentgenographic findings. In 2 cases initial erythema nodosum was present. The hilar adenopathies were usually of large size; the usual period for complete regression was twelve to eighteen months. Incidents were mostly prone to occur within the first six months. There was one case of fatal tuberculous meningitis in the second month; 2 of bilateral pleurisy, one of which was associated with ascites; and 4 of unilateral pleurisy. Other cases showed the development of new pulmonary foci of a transitory or protracted nature. The patients were kept on strict rest for about one year. Normal activity was resumed at the earliest after eighteen months, most often only after two years.—*A propos de 22 cas d'adénopathie médiastinale tuberculeuse du jeune adulte suivés au moins un an, J. Le Melletier, M. Delord, M. Heckenroth, & J. Giron, Rev. de la tuberc., 1949, 13: 423.*—*(V. Leites)*

Pulmonary Segments.—The pulmonary segments were mapped in a variety of diseases by means of bronchograms and occasionally by bronchoscopy. The terminology of the French Society for Respiratory Pathology was used throughout. When the apical segment of the upper lobe of the right lung was affected by tuberculosis limited to it, the segment often appeared to be retracted. A lesion of the anterior segment of the upper lobe viewed from the front ordinarily seemed to extend much farther toward the base of the lung than would be supposed and even to extend into the middle lobe area. A tuberculous lesion of the anterior segment of the right upper lobe often had the appearance of a large mushroom

in the hilar region and viewed laterally resembled a pistol. Apical pneumonia often was limited to the posterior segment of the upper lobe. Tuberculosis of this segment sometimes gave rise to retraction and produced a concave lower segmental border in spite of extension of the disease into the adjacent segment. This segment, especially its external portion, occasionally was the site of a pulmonary abscess. Characteristic shadows in segments of the middle lobe were due to tuberculosis, neoplasm, or acute inflammation. Acute pneumonia in the lower lobe commonly involved the posterior segment. While tuberculosis and cancer might involve any of the segments, abscesses affected especially the axillary segment; virulent inflammatory processes occurred most often in the middle lobe of the right lung, the lingula in the left lung, or the internal segment of the lower lobe.—*Quelques aspects radiologiques des segments pulmonaires normaux et pathologiques, A. Meyer, J. Dubois de Montreynaud, & J. Sistier, Le Poumon, July–August, 1949, 5: 257.—(A. T. Laird)*

Liver Biopsy in Miliary Tuberculosis.—In a case suspected of miliary tuberculosis, a punch biopsy of the liver revealed characteristic tubercles.—*Punch liver biopsy in the diagnosis of miliary tuberculosis, C. G. Graddock & H. C. Meredith, Jr., New England J. Med., October 6, 1949, 241: 527.—(A. G. Cohen)*

Granulocytes in Tuberculosis.—Granulocytes were normal in the newborn and in persons with a negative tuberculin reaction. They were found modified in individuals who had a positive tuberculin reaction but were clinically and radiologically free of tuberculosis. In the latter there were about 56 per cent normal leukocytes containing a small number of fine granulations, 33 to 41 per cent intermediary forms with granulations increased in number but not in size, and 1 to 3 per cent abnormal leukocytes with granulations increased in number and size. The normal blood picture as determined in the newborn and in young students contained 3 and 9 per cent intermediary forms, respectively. In active primary tuberculosis the intermediate forms constituted 50 to 90 per cent of the leukocytes. The pathological forms sometimes rose to 10 to 20 per cent and more. In miliary tuberculosis and tuberculous meningitis the normal forms almost disappeared; the pathological granulocytes might reach 40 to 50 per cent. A parallelism was observed between the success of streptomycin treatment and the return of the granulocytes to normal. In young adults and newborn children injected with BCG, the granulocytes showed definite changes similar to those in tuberculin-positive individuals. The percentage of intermediate forms was 34 and 60, respectively.—*Les granulations des polynucléaires neutrophiles dans la primo infection tuberculeuse de l'enfant, P. Verger, J. Bentegeat, & P. Lativille, Rev. de la tuberc., 1949, 13: 454.—(V. Leites)*

Pneumothorax Complicating Pneumoperitoneum.— A case of pulmonary tuberculosis was treated with artificial pneumoperitoneum. It was found that, when the patient sat up, the air entered the right pleural cavity, but not the left. It was not possible to demonstrate the defect by thoracoscopy or other means. It is suggested that most of these cases are due to the abnormal persistence of a pleuroperitoneal canal.—*Spontaneous pneumothorax complicating artificial pneumoperitoneum, E. G. S. Lumsden, Thorax, September, 1949, 4: 147.—(A. G. Cohen)*

Pleural Pneumonectomy.—The operative risk of pleural pneumonectomy is much greater than that of simple pneumonectomy in the presence of a free or loosely adherent pleura. In some cases decortication alone requires more than two hours. The procedure is particularly dangerous on the mediastinal side entailing a risk of injury to large vessels and nerves, and danger of ventricular fibrillation from too violent traction on pleuropericardial adhesions. In cases of fibrothorax all anatomical landmarks may disappear so that the identification of the various structures is difficult and hazardous. In the postoperative period, infection and dissemination of tuber-

culosis constitute the main dangers. The indications for the operation may be predominantly pleural or pulmonary. The operation is considered contraindicated after the age of 40.— *La pleuro-pneumonectomie, mode de traitement radical de la pleurésie purulente tuberculeuse associée a des lésions du parenchyme pulmonaire, M. Berard & P. Juffin, Rev. de la tuberc., 1949, 13: 589.—(V. Leites)*

Results with Collapse Therapy.—During the past eight years tuberculous patients at S. Paulo have been treated with (*1*) extrapleural pneumothorax, (*2*) thoracoplasty, and (*3*) phrenic paralysis with pulmonary resection. Extrapleural pneumothorax was tried in 186 cases; 63.4 per cent were "cured" and 9.1 per cent improved. The recovery rate was much lower in patients treated in dispensaries than in those cared for in private practice or in the sanatorium. When this method was employed for absolute indications, results in both unilateral and bilateral cases were about twice as good as when it was used for relative indications. In late stages of the disease, the method is followed by a varying percentage of spreads or progression. Thoracoplasty by Alexander's method was undertaken in 385 patients and completed in 363. Recovery occurred in 89.6 per cent of the 327 cases of unilateral excavated lesions and the mortality within two months after operation was only 2.1 per cent. Scoliosis following this operation detracts from its value except in selected cases. With hemidiaphragmatic paralysis, "cures" were obtained in 45.8 per cent of 146 cases of lesions in the lower lobe; results were especially good in cases of unilateral and small cavitary lesions. Among 44 of these cases in which a lower lobectomy might have seemed indicated, the phrenic operation succeeded in 59 per cent but bilateral extension occurred in 27.2 per cent. This shows the advantage of postponing pulmonary resection until after hemidiaphragmatic paralysis has been tried. Streptomycin should invariably be associated with any collapse therapy method. Results with any of these methods are greatly influenced by adequate rest and diet. Pulmonary resection was tried in only 7 cases and completed in 6. Three patients have died and 3 are well, but tubercle bacilli disappeared from the sputum in only one. No comparison could be drawn between surgical collapse therapy and resection as the procedures are supplementary.—*Resecções pulmonares e colapsoterapia cirúrgica no tratamento da tuberculose pulmonar, E. Etzel, Clín. Tisiol., April-June, 1949, 4: 165.—(A. A. Moll)*

Lucite Spheres for Pulmonary Collapse.—One-inch Lucite spheres were sterilized overnight in Zepheran before use. All patients received penicillin two days before operation and a week postoperatively. Earlier patients were treated with a two-stage operation, first establishing an extrapleural pneumothorax maintained by air for two weeks and then inserting the Lucite spheres. Later patients were treated with a one-stage procedure which usually was followed by recurrent fluid. More recently tube drainage of the extrapleural space has been adopted. The indications for this operation are essentially those for thoracoplasty and especially in those conditions where thoracoplasty cannot be done. The only contraindications to this operation are very thin-walled or peripheral cavities. The advantages are that there is (*1*) no deformity of the thoracic cage, (*2*) less shock and less risk, (*3*) a fair chance to close or decrease the size of the cavity and to stabilize the mediastinum, (*4*) preservation of pulmonary function (*5*) no paradoxical motion, (*6*) better collapse, and (*7*) a reduction of the period of hospitalization. The 52 cases reported are too recent to permit final conclusions, but it is felt that Lucite extrapleural plombage may gain a wider application in the treatment of pulmonary tuberculosis than thoracoplasty. Sputum has become negative in 71 per cent of the cases and is still positive in 29 per cent. Of the 52, 14 cases are considered as arrested, 22 cases apparently arrested, and 16 cases are regarded as active.—*The use of Lucite in surgical treatment of pulmonary tuberculosis, N. C. T. Chang & A. S. DeFuentes, Chinese M. J., March, 1949, 67:* 119.—(*L. Hyde*).

Surgery in Bone and Joint Tuberculosis.—Bone and joint tuberculosis associated with pulmonary tuberculosis was treated surgically in 40 patients. None of the patients had positive sputum at the time of intervention; 11 had arrested disease; 11 others had had active disease recently but it had remained stable for a few months prior to operation. Five patients were under pneumothorax treatment; 13 had active pulmonary tuberculosis at the time of intervention but had showed evidence of regression. In 38 of the 40 patients the pulmonary condition remained unchanged after surgery. One patient had exacerbation of his pulmonary lesions nine months later but it was not attributed to the surgical procedure. One patient died of generalized tuberculosis. The operations were performed for 25 cases of Pott's disease, 6 cases of hip joint tuberculosis, 5 cases of tuberculosis of the knee, 2 cases of osteo-arthritis of the foot, and 2 cases of elbow tuberculosis. It is emphasized that the favorable results were obtained because surgery was performed in a sanatorium on patients well prepared by orthopedic immobilization, open-air treatment, and heliotherapy.—*La chirurgie osteo-articulaire des tuberculoses mixtes de l'adulte, J. Sarroste, Ciosi-Frenay, & P. Blind, Rev de la tuberc., 1949, 13: 440.—(V. Leites)*

Round Foci in Childhood Tuberculosis.—In tuberculous children several types of round pulmonary lesions may be demonstrated roentgenographically. (*1*) "False" round foci are lesions such as fibrin bodies persisting after re-expansion of pneumothorax, filled cavities, or round areas of pneumonitis. (*2*) Early infiltrates occasionally have a rounded shape. They occur most frequently at the age of puberty. (*3*) "Secondary" round foci occur after the primary phase in the period of dissemination. They are solitary, of low density, and show a marked tendency to spontaneous and rapid absorption. (*4*) Round primary foci may absorb or develop punctate calcifications within the round density. (*5*) A special form of round shadow is described as "exudative focus." It is usually small, soft, and sometimes hard to visualize on the roentgenogram; it may occur in any part of the lung fields at any stage of the disease. It may undergo complete regression but sometimes excavation develops.—*Étude radiologique des foyers ronds pulmonaires chez l'enfant tuberculeux, P. Lowys & G. Lepercq, Rev. de la tuberc., 1949, 13: 410.—(V. Leites)*

Clinical Studies, Nontuberculous Diseases

Eosinophilic Pneumonia.—Twenty cases of transient eosinophilic pulmonary infiltration were discovered when the men in a cavalry reserve unit were fluoroscoped routinely prior to discharge. The total number of men in this unit is not stated. None of the 20 patients was sufficiently ill to report on sick-call, and none had fever. The radiographic picture in 15 cases was that of a large, irregular density without sharp demarcation. One case showed many small, round foci; one, a sharply demarcated lesion; and 3 showed irregular densities blending with the hilar shadow. All lesions disappeared within two to eight days. Eosinophilia ranged from 4.5 to 26 per cent. Physical signs were almost completely absent and the erythrocyte sedimentation rate generally was normal. The intracutaneous test with *Ascaris* extract was positive in 60 per cent, but in some cases the test could only be done after the infiltration had disappeared, i.e., not at the height of the illness. Only one of 17 cases showed *Ascaris* eggs in the stool, but following two courses of treatment with vermifuge (Chenosan) *Ascaris* eggs were demonstrated in 45 per cent. Ten of the 20 patients showed negative Mantoux tests. A thorough investigation of the living and eating habits was made. It was felt that there were several factors which predisposed to *Ascaris* infestation and development of eosinophilic lung infiltrations. It was discovered, for example, that the truck in which the vegetables were carried was also used for troop transport when necessary. Changes in the handling of rations should reduce the incidence of infestation. (*1*) The purchase of vegetables and salad greens which have been "top" fertilized

should be discouraged. (*2*) Kitchen equipment should not be used for other purposes. (*3*) The kitchen personnel should be clean and there should be a permanent kitchen crew instead of a rotating crew. (*4*) All salad greens and vegetables should be rinsed in salt water solution before preparation.—*20 Fälle von eosinophilem Lungeninfiltrat in einer Kavallerie Rekrutenschule, M. Wallertshauser, Schweiz. med. Wchnschr., October 22, 1949, 79: 1002.*—(*H. Marcus*)

Chronic Suppurative Pneumonia.—Twenty-five cases of chronic suppurative pneumonia were observed during the recent war in a military hospital in the Middle East and occurred in persons of many different nationalities. The duration of illness ranged from three to twenty-one months with an average duration of ten months. There was no past history of pulmonary disease but in 6 cases there was some abnormality or disease of the upper respiratory tract. The onset was acute in 15 cases, with chest pain, cough, and fever. In 10 cases, the onset was gradual, with cough and increasing fever. In all except one, there was copious, frankly purulent sputum from the outset; in 13, a fetid odor was noted. The fever was usually intermittent for a few weeks and then reappeared in recurring bouts. It usually was not excessive. Between bouts the general condition was good. There was cough in all, with the daily expectoration ranging from 50 to 1,100 cc. In all but 4, the sputum was fetid at one time or another. Hemoptysis was frequent. In 23 cases the fingers were clubbed; hypertrophic osteo-arthropathy was present in one case. Physical findings were variable. The total white blood count often did not exceed normal; the highest was 19,800 per cu. mm. The differential counts were approximately normal. The sputum showed a mixed growth consisting of *Str. viridans, Str. hemolyticus, M. catarrhalis, Pneumococcus,* and *Staph. aureus.* Numerous examinations for tubercle bacilli in each case were negative. Bronchoscopy was performed for all but 5 cases; this showed redness and edema of the bronchi in the affected areas, with pus welling up from the branches. Initial roentgenograms showed consolidation of a segment in 12, of a whole lobe in 7, of most of one lung in one, and scattered throughout a lobe in 2 cases; early films were not taken in 3. The initial lesion was in the right lung in 15 and in the left in 7. A cavity appeared within three weeks in 5, within three months in 9 more, and eventually in 5 more; cavities never appeared in 6. The behavior of the lesions varied. Spread occurred by direct extension, to which fissure lines were no barrier. The lesions often remained stationary for two to three months during which time there was clinical improvement. Then clinical relapse and radiographic spread occurred, in 7 cases to parts of the lung not in direct contact with the lesion. Pathological data from resection specimens or necropsy were available in 12 cases. Grossly, the lung was airless, gray, and rubbery, and contained one or more cavities. The pleura was thick and shaggy over the affected areas; the fissures were obliterated. Microscopically there was marked suppuration, infiltration, consolidation, and fibrosis. The bronchi were also extensively involved. The patients came under care three weeks to nine months after the onset. All received postural drainage and sulphonamide drugs; 8 received penicillin after it became available. One case cleared up entirely; another became well except for slight residual expectoration. Two became well clinically but there was gross fibrosis of the previously involved areas; bronchograms showed bronchiectasis in these areas. In the other cases, there was alternate remission and relapse. External drainage was performed in 6 cases with no benefit. Lobectomy was performed in 9 and pneumonectomy in one; there were 4 operative deaths. Five patients were cured; the other became well except for slight expectoration. Thus, in the whole series there were 6 deaths (4 operative); 7 patients had good results (6 operative), one was greatly improved, 2 were well but had chronic fibrosis with bronchiectasis, and 9 were unimproved. It is believed that the distinction between putrid and nonputrid suppuration is not valid but that nonspecific

pulmonary suppuration is a single disease. At one extreme there is the uncomplicated abscess; at the other, the pneumonic aspect predominates. Except for the simple abscess which responds to drainage, resection is the treatment of choice.—*Nonspecific suppurative pneumonia, A. Logan & H. Nicholson, Thorax, September, 1949, 4: 125.*—(*A. G. Cohen*)

Pulmonary Brucellosis in Brazil. Pulmonary brucellosis was diagnosed in 4 patients from different parts of Brazil. In 3 of them, because of an incorrect diagnosis of pulmonary tuberculosis, pneumothorax treatment was tried. One of the cases was cavitary, which is rather unusual in this condition. Partial surveys have shown the wide prevalence of *Brucella* infection in cattle in such states as Rio Grande do Sul, Minas Gerais, and S. Paulo. Since the first human case was described in 1932, human cases of brucellosis reported in Brazil exceed 500.—*Brucelose pulmonar, R. Fernandes, Clín. Tisiol., April-June, 1949, 4: 217.*—(*A. A. Moll*).

Nonoccupational Berylliosis.—Chronic pulmonary granulomatosis as seen in beryllium workers was observed in 11 people residing in the vicinity of a commercially owned plant producing beryllium compounds. Diagnosis was based on careful clinical and roentgenologic examination and pathologic examination when available. The findings were reviewed by specialists who had become familiar with the disease. None of these affected persons had an occupational exposure to beryllium. A study was set up to determine the relationship between the incidence of cases and the levels of atmospheric contamination. An extensive air-analysis program was carried out. Ten of the persons resided within three-quarters of a mile from the plant. The distribution of the cases indicates that the incidence of disease was a function of the concentration of beryllium to which the residents were exposed. One patient lived almost two miles from the plant and was the wife of an employee of the plant. Her disease is believed to have resulted from the handling of the contaminated clothing of her husband. The average concentration of beryllium three-quarters of a mile from the plant is estimated as ranging from 0.01 to 0.1 microgram per cubic meter. The cases appear to have resulted from exposure prior to 1946 when the three-quarter-mile-concentration is estimated to have been approximately 0.1 microgram per cubic meter. The average daily concentrations of beryllium in the vicinity of a plant producing beryllium should be limited to 0.01 microgram per cubic meter. There is no justification for applying these data as criteria in judging the hazard of exposed workers in the beryllium industry. The incidence of berylliosis within the plant under study was low. The neighborhood contamination may have an enhanced toxicity because of the smaller particle size than would be expected within the plant.—*Nonoccupational berylliosis, M. Eisenbud, R. C. Wanta, C. Dustan, L. T. Steadman, W. B. Harris, & B. S. Wolf, J. Indust. Hyg. & Toxicol., September, 1949, 31: 282.*—(*H. R. Nayer*).

Human Pseudotuberculosis.—The rare and always fatal illness produced by *Pasteurella pseudotuberculosis rodentium* has been described in only 17 patients in the world literature. Two cases are added in this report. Pseudotuberculosis is an infectious, rapidly fatal illness of adults. The predisposing causes are obscure but it has been noted that in many cases the infection was associated with mild or severe hemochromatosis. The inference may be that disturbance of pigment metabolism and cirrhosis predisposes humans to the development of an illness which usually affects only rodents. Both cases described in this paper were rapidly fatal with a septic course which was not influenced by chemotherapeutic and antibiotic agents. Autopsy showed the characteristic gross lesions in the liver and other organs. The organisms isolated from both cases gave all the morphological reactions of *Pasteurella pseudotuberculosis rodentium*, but the bacillus was nonpathogenic for all animals in which it was tested. The test animals included guinea pigs, mice, rats,

rabbits, and pigeons.—*Ueber Pseudotuberkulose beim Menschen, A. Hässig. J. Karrer, & F. Pusterla, Schweiz. med. Wchnschr., October 15, 1949, 79: 971.*—(*H. Marcus*)

Nocardiosis.—The 3 patients reported were infected with Actinomyces which were isolated from the lesions and shown to belong to the relatively rare aerobic, variably acid-fast group of the Nocardia. The importance of the actinomycotic infections lies in the possibility of their being confused with tuberculosis. Nocardiosis should be considered in all patients with obscure or unusual chronic infections, especially when repeated attempts to demonstrate the tubercle bacillus have failed. The treatment of choice in the aerobic type of actinomycotic infection appears to be sulfadiazine or other sulfonamides, rather than antibiotics such as penicillin and streptomycin. *Nocardiosis, with a report of three cases of actinomycosis due to Nocardia asteroides.—F. C. Tucker & E. F. Hirsch, J. Infect. Dis., July–August 1949, 85: 72.*—(*F. G. Petrik*).

Pulmonary Aspergillosis.—Previously reported cases of pulmonary aspergillosis occurred exclusively in individuals who had intimate contact with birds or grains. Two cases are reported in which the clinical course had been typical of pneumoconiosis as seen in coal miners and that diagnosis was confirmed at necropsy. In addition, there were areas of infection caused by *Aspergillus fumigatus.* The association of the two conditions is rare. No obvious source of infection underground could be adduced.—*Pulmonary aspergillosis in coal workers, A. G. Heppleston & S. R. Gloyne, Thorax, September, 1949, 4: 168.*—(*A. G. Cohen*)

Coccidioidomycosis in Children.—A series of 10 cases of coccidioidomycosis from the heart of an endemic area (Kern County, California) shows the various lesions which may occur in infants and children. These include pulmonary lesions, pulmonary lesions complicating tuberculosis, pulmonary lesions with the pneumonia of pertussis, pleurisy with effusion, spina ventosa, meningitis, disseminated lesions, spinal involvement, and osteomyelitis with dermal lesions. Chlamydospores are highly infective for the lung, but patients are not directly infectious from pulmonary lesions to contacts. An open wound may be contaminated from a draining sinus. Over 95 per cent of the active cases having a positive coccidioidin skin test show primary lung lesions. The complement fixation test demonstrates the progress of a lesion; the precipitin test indicates its recency. Over 90 per cent of the lung lesions heal. No case of miliary coccidioidomycosis has been reported in children. Meningitis is not uncommon, lasts about five months, and is fatal. Infants of mothers with active disease have not shown congenital lesions, but the complement fixation test may be positive from passively transferred humoral antibodies.—*Coccidioidomycosis: Case studies in children, R. Cohen, Arch. Pediat., June, 1949, 66: 241.*—(*W. H. Oatway, Jr.*)

Obstetrical Coccidioidomycosis.—Disseminated coccidioidomycosis was a cause of maternal deaths in 4 cases. In 2 of the infants, complement fixation tests for coccidioidomycosis showed weak titers which were interpreted as evidence of passive transfer of antibodies. Typical granulomas of coccidioidomycosis were demonstrated histologically in the placenta from another case.—*Maternal deaths from coccidioidomycosis, L. E. Smale & J. W. Birsner, J.A.M.A., August 6, 1949, 140: 1142.*—(*H. Abeles*)

Pleural Paragonimiasis.—Paragonimiasis is an endemic parasitic disease in the Far East. A 35-year-old Chinese man who had *Paragonimus* ova in his sputum repeatedly was subjected to thoracotomy with biopsy of the parietal pleura. The tissue revealed *Paragonimus* ova with acute and chronic inflammation. It is believed that one or more subpleural parasitic cysts ruptured into the pleural cavity. No similar case has been reported previously.—*Pleural paragonimiasis complicated by empyema thoracis: Report of a case, S. N. Koo*

& D. L. Woo, Chinese M. J., April, 1949, 67: 211.—(L. Hyde)

Infarcts in Opiate Addiction.—An addict who had used opiates intravenously for eighteen years had shadows in the chest roentgenograms suggesting disseminated or miliary pulmonary disease. These lesions proved to be scars from multiple pulmonary infarcts.—*Nodular pulmonary densities due to scars of multiple pulmonary infarcts, C. E. Grayson, Am. J. Roentgenol., August, 1949, 62: 208.—(T. H. Noehren)*

Circulation in Emphysema.—Emphysema and congestive cardiac failure have many symptoms and signs in common, especially dyspnea and cyanosis, so that a differential diagnosis is often difficult. Usually, in cardiac failure, the liver is enlarged and there is edema. However, in emphysema, the liver is pushed downward and differentiation from enlargement may be difficult. Four groups of patients were studied: (*1*) emphysematous, 25 cases; (*2*) emphysematous with heart failure, 12 cases; (*3*) normal, 40 cases, and (*4*) those having rheumatic heart disease with failure, 40 cases. Cases of pure emphysema are very hard to find since, after middle age, arteriosclerosis and hypertension are so frequent. For the same reason cardiac failure due solely to emphysema is rare; cases were selected in which emphysema was the chief cause. The 37 patients with emphysema all showed the Christie pattern of breathing. All procedures were carried out in 45-degree recumbency. The venous pressure was taken without and with abdominal pressure. The circulation time was determined with Decholin (arm-tongue) and with ether (arm-lung). In patients with emphysema but without failure (group 1) the venous pressure was elevated but did not increase with abdominal pressure. The arm-tongue and lung-tongue circulation times were less than in the normal controls (group 3) while the arm-lung time showed no statistical difference from normal. In patients with heart failure due mainly to emphysema (group 2) the venous pressure was elevated and rose higher with abdominal pressure. The arm-tongue and arm-lung times were greater than in groups 1 and 3. The lung-tongue time, which is the most significant evidence for left ventricular failure, was greater than in group 1 but not statistically different from group 3. Thus on the average circulation time in uncomplicated emphysema is faster than normal; the appearance of cardiac failure slows it to within normal limits. In individual cases of emphysema, evidence for the appearance of failure may be gleaned from slower rates than those previously recorded. In the patients with mitral disease and heart failure (group 4) the arm-tongue time was twice that in emphysema with failure. An elevated venous pressure in emphysema is not necessarily an evidence of failure but an increase with abdominal pressure is diagnostic.—*Circulatory dynamics in emphysema, A. D. Gillanders, Quart. J. Med., July, 1949, 18: 263.—(A. G. Cohen)*

Emphysema from Tracheal Puncture.—In 2 infants, nine and seven days old, attempted venipuncture of the jugular vein resulted in perforation of the trachea. Fatal interstitial and mediastinal emphysema ensued. The exact status was not clear until autopsy. One infant had notable emphysema in the tissues of the neck, head, and mediastinum; the other had air in a similar distribution, as well as in both pleural spaces. Greater care is necessary in performing venipunctures in the cervical area.—*Fatal interstitial and mediastinal emphysema following accidental needle perforations of the trachea during jugular venipuncture, P. Goldstein, Am. J. Dis. Child., September, 1949, 78: 375.—(W. H. Oatway, Jr.)*

Orthoxine in Bronchial Asthma.—Orthoxine (ortho - methoxy - β - phenyl - isopropylmethylamine hydrochloride) is a new synthetic bronchodilator substance which is active when taken by mouth. There are no strong vasopressor or central nervous system-stimulating effects. The average adult dose effective orally is from 100 to 200 mg. The vital ca-

pacity was studied in 14 patients and frequently was increased with this dosage. Relatively little alteration in cardiac rate was seen in the 18 patients examined for this effect. A slight drop in systolic blood pressure, more pronounced in those with hypertension, occurred in some patients. Side effects were mild and infrequent although nausea and mild central nervous system-stimulating effects were seen occasionally. Many patients who were extremely intolerant to ephedrine experienced no difficulty after a clinically effective dose of Orthoxine. The clinical effectiveness of the new drug in mild and moderately severe bronchial asthma and its lack of action on the cardiovascular and central nervous systems suggest its use in place of ephedrine, especially where hypertension, cardiovascular disease, and side effects preclude the use of ephedrine.—*Observations on the action of orthoxine in patients with bronchial asthma, S. Friedlaender & A. S. Friedlaender, Ann. Allergy, September–October, 1949, 7: 685.*—*(B. Hyde)*

Valvulotomy for Pulmonary Stenosis.—Although the Blalock short-circuiting operation has been successful in many cases of pulmonary stenosis, a correction of the lesion itself might be preferable. Direct valvulotomy has been performed successfully on 5 patients, the stenotic valve being divided by a special valvulotome inserted through the wall of the right ventricle and passed into the pulmonary artery. The operation has been attempted in a total of 10 cases; in 3, the heart failed soon after the chest was opened and all 3 patients died. In the last of these 3 cases, all efforts at resuscitation of the heart were unsuccessful and valvulotomy finally was performed in spite of the heart's status. The heart at once revived and its powerful action was fully restored. Although this patient died because of cerebral damage, the cardiac revival demonstrated the feasibility of relieving the stenosis after the heart's action had ceased. Direct resection has been carried out successfully through the wall of the right ventricle in 5 cases of pulmonary infundibular stenosis. One other patient died and her lesion was found to be situated just below the valves.—*The surgery of pulmonary stenosis, R. C. Brock, Brit. M. J., August 20, 1949, no. 4624: 399.*—*(R. W. Clarke)*

Surgical Treatment of "Cardiac Lung."—Three operations were devised for the management of the "cardiac lung": (*1*) anastomosis of a pulmonary vein with the subclavian artery, the splenic artery, or its homonomous vein; (*2*) tricuspid valvulotomy; and (*3*) ligation of the inferior vena cava below the renal veins. These last procedures were attempted in patients who suffered from heart failure and permanent orthopnea and who were no longer responsive to medical treatment. An immediate and dramatic improvement was the rule over a period of six months, which was the longest observation time. (Authors' summary) —*Surgical treatment of the "cardiac lung," ligation of the inferior vena cava and/or tricuspid valvulotomy, P. Cossio & I. Perianes, J.A.M.A., July 2, 1949, 140: 772.*—*(H. Abeles)*

Shunt for Mitral Stenosis.—A new operative procedure for the relief of recurring pulmonary edema secondary to advanced mitral stenosis consists of an extracardiac shunt to provide an outlet from the high pressure left auricle-pulmonary vein area into the systemic venous bed. This is accomplished by anastomosing the dorsal segment branch of the right inferior pulmonary vein to the azygos vein. The operation was carried out in 5 patients. Three patients have remained free from attacks of pulmonary edema during follow-up periods of four, five, and twelve months, respectively. One patient succumbed on the eleventh postoperative day to a severe recrudescence of rheumatic fever. The fifth patient has been followed for too short a period to permit conclusions as to the success of the operation.—*A venous shunt for advanced mitral stenosis, E. F. Bland & R. H. Sweet, J.A.M.A., August 20, 1949, 140: 1259.*—*(H. Abeles)*

Arteriovenous Fistula.—Abnormal communication between an artery and a vein in the lung produces a clinical syndrome consisting of cyanosis, clubbing of the fingers and toes, bruit, and polycythemia. Its possibility should be considered in any patient with unexplained polycythemia and associated symptoms due to disturbed oxygenation of the blood. An analysis was made of 26 cases from the literature and one from the practice of the author. The characteristic findings common to almost all the cases were cyanosis, dyspnea, clubbing of the digits, and thoracic bruit. Associated findings of visible vascular anomalies, chest pain, hemoptysis, absence of cardiac enlargement, weakness, dizziness, faintness, and fatigue occurred with sufficient frequency to warrant their inclusion in the syndrome. The roentgenographic findings consisted primarily of a round, smooth, soft tissue tumor mass usually in the lower lung field. The hilum of the involved side appeared denser than the opposite one due to the added vascular bed. Two large sinuous blood vessels usually were seen arising from the hilum and converging on the soft tissue mass in the parenchyma. One of these showed definite pulsations synchronous with the pulmonary artery. The other, the vein, showed minimal or no pulsation. The Valsalva and Müller tests occasionally helped define the lesion. The significant laboratory findings were the polycythemia with increased hemoglobin and hematocrit values, but with a normal white blood cell count. This is in contrast to polycythemia vera where the white blood cell count is not elevated.—*The syndrome of arteriovenous fistula of the lung, P. Crane, H. H. Lerner, & E. A. Lawrence, Am. J. Roentgenol., September, 1949, 62: 418.*—(*T. H. Noehren*)

Respiratory Tract Obstructions.—Two cases of congenital tracheal stenosis associated with malformation of the tracheal cartilages are reported. The normal infantile trachea usually has a fairly fixed caliber but in some instances transient narrowing of the trachea may occur, apparently due to soft tracheal cartilages. Abnormal cervical and mediastinal masses, a large thymus, or a vascular ring impinging on the trachea will produce stenosis of the trachea depending in large part upon the development and pliability of the tracheal cartilages. (Author's summary)—*Congenital obstructions of the respiratory tract: I. Tracheal malformations, W. A. Evans, Jr., Am. J. Roentgenol., August, 1949, 62: 167.*—(*T. H. Noehren*)

Respiratory Tract Obstructions.—Two cases of bronchial obstruction due to congenital malformations are reported. In one there was collapse of the bronchial lumen with atelectasis of the lung, presumably due to a deficiency of the cartilage in the wall. In another there was partial obstruction due to cysts in the brnochial lumen with defects in the cartilaginous structures of the bronchial wall. Comparison has been made with similar cases reported in the literature. Three cases of congenital expansile air cysts in the lungs treated surgically have been reported. Surgical removal of an expanding segment of lung, whether due to obstructive emphysema or cystic disease, is feasible and desirable when the expanding segment threatens the function of the remaining lung. (Author's summary)—*Congenital obstructions of the respiratory tract: II. Bronchial malformations, W. A. Evans, Jr., Am. J. Roentgenol., August, 1949, 62: 177.*—(*T. H. Noehren*)

Carcinoma of Lung.—Review of 1,000 cases of cancer of the lung observed at a chest center between 1933 and 1949 showed that 91 per cent of the cases were male. The average age was 45 to 55 in males, slightly less in females. There was no significant occupational history. The right lung was involved slightly more often than the left. Three histological types of carcinoma were recognized: undifferentiated oat-cell, epidermoid, and adenocarcinoma, listed in the order of frequency. There was no relationship between the histological type and age. The epidermoid type often was complicated by cavities and abscesses; the prognosis was worst in the undifferentiated type. The early lesions often were asymptomatic.

When symptoms appeared they were, in descending order of frequency, cough, pain, dyspnea, lassitude, hemoptysis, loss of weight, fever, wheezing, congestive failure, hoarseness, expectoration, clubbing, and dysphagia. There was an average interval of eight months from the onset of symptoms to diagnosis and this has not been shortened with the passage of time. Radiographically, there was collapse in 64, a dense shadow at the hilus in 17, a cavity with fluid level in 10, and a solitary mass in the periphery in 4 per cent. Tomograms usually showed (*1*) a mass or an area of increased density at the apex of the pyramid of collapsed lung tissue, or (*2*) a mass protruding into the lumen of a bronchus. The interior of cavities had a corrugated appearance. Bronchography, performed in a few cases, sometimes showed a block. Bronchoscopy was diagnostic in many. Criteria of inoperability were found to be dissemination of lesions, proximity to the carina, widening of the carina, extension to the mediastinum, and recurrent nerve paralysis. Phrenic paralysis and bloody pleural fluid were not absolute contraindications but distortion of the esophagus was. Preoperative respiratory exercises, postural drainage, and penicillin administration were important. The most frequent postoperative complications were bronchial fistula and empyema. Exploratory thoracotomy was carried out in 353 of the 1,000 cases; pneumonectomy was performed in 202. Of these 54 died within a month; 68 more died of metastases, and 18 of other causes. The author now gives roentgen therapy to all inoperable cases. Opiates and cocaine are given for palliation of pain and, if severe, paravertebral injection of anesthetics or cordotomy is indicated. Palliative pneumonectomy may be performed for suppuration and osteoarthropathy.—*Cancer of the lung, G. A. Mason, Lancet, October 1, 1949, 2: 587.*—(*A. G. Cohen*)

New Uses of Kymography.—New kymographic methods throw more light on the cardiopulmonary circulation in man. A single-slit kymograph records the passage through the auricular cavities of a radiopaque substance introduced intravenously. Use of this device determines the rate of circulation in the lungs as well as in the heart or in any of the pulmonary lobes. Another improved kymographic technique records simultaneously horizontal and vertical movements of the chest. Through its help it has been verified that mediastinal displacement during inspiration is invariably toward the collapsed side in patients with pneumothorax. Another new kymograph has cross-slits arranged like a net in the grid; the film moves clockwise instead of lineally. This instrument records the displacement of cavitary walls and consequently the traumatic effect of respiration on cavities.—*Novas apliçacões da quimografia, L. de Carvalho, Clin. Tisiol., April-June, 1949, 4: 135.*—(*A. A. Moll*)

Antimicrobial Therapy

Streptomycin Resistance and Cavities.—Among 116 patients treated with streptomycin there were 98 cases of progressive pulmonary tuberculosis, 14 of endobronchial tuberculosis with cavitation, 20 of tuberculous laryngitis, and 2 of intestinal tuberculosis. Tubercle bacilli were found in the sputum of all patients. In 100 cases the bacilli isolated before treatment were sensitive to streptomycin. The daily dose of streptomycin was usually 1.0 Gm. The cases were divided into 3 groups: (*1*) cavitary, no collapse therapy; (*2*) no cavity; and (*3*) cavitary lesion, collapse therapy instituted prior to drug therapy. Streptomycin-resisant organisms were isolated at the close of therapy in 40 per cent of group 1, in 11 per cent of group 2, and in 10 per cent of group 3. The conclusions were that resistance is more likely to appear when a cavity is present and that the size of the cavity is also a factor.—*The relation of cavity to the development of streptomycin-resistant tubercle bacilli in pulmonary tuberculosis, R. S. Mitchell, New England J. Med., September 22, 1949, 241: 450.*—(*A. G. Cohen*)

Streptomycin Therapy.—Streptomycin was tried in 50 varied cases of pulmonary tuberculosis from October, 1947 to June, 1948.

In 30 the drug was used by itself and in the remaining 20 it was associated with collapse therapy. There was recovery in 8 per cent, marked clinical and roentgenological improvement with disappearance of tubercle bacilli from the sputum in 42 per cent, marked clinical improvement with disappearance of bacilli but no roentgenographic changes in 8 per cent, clinical improvement without changes in roentgenograms or sputum in 20 per cent, and no change or deterioration in 22 per cent. Best results (40 per cent recoveries) were obtained in minimal exudative lesions. In the 24 far advanced cases no recoveries occurred, but 6 cases improved considerably and 7 improved somewhat. In 85.7 per cent of the 21 moderately advanced cases good results were obtained. Total dosage of the drug averaged 90 Gm. in a thirty- to ninety-day period, the daily dose varying from 1.0 to 1.5 Gm. Vestibular complications developed in 76 per cent of cases. The symptoms subsided gradually in all of the 38 affected patients, but treatment had to be discontinued in 13. Skin eruptions occurred early during the treatment in 6 cases; they yielded promptly to benadryl.—*A estreptomicina no tratamento da tuberculose pulmonar, N. Bethlem, Clin. Tisiol., April–June, 1949, 4: 243.*—(*A. A. Moll*)

Streptomycin for Tuberculous Meningitis.—Intensive intrathecal streptomycin therapy in association with parenteral treatment is essential for the successful management of tuberculous meningitis. The irritating effect of the streptomycin solutions commonly used is attributed to the fact that they are highly hypertonic. A 1:10 dilution of streptomycin in saline has a molecular concentration five times higher than that of the cerebrospinal fluid. The authors add enough distilled water to obtain an isotonic solution. In this manner intrathecal streptomycin was given without major incidents in two daily injections of 0.1 Gm. during the first month, one daily injection during the second month, and one injection every other day during the third month. Of 30 cases treated in this manner, 10 have a follow-up longer than one year and have no demonstrable sequelae. There were 3 deaths. The remaining patients are alive in good condition while still receiving treatment.—*Le traitement des meningites tuberculeuses par la streptomycine, R. Rivoire & A. Colleau, Presse méd., July 6, 1949, 57: 633.*—(*V. Leites*)

Willis Phenomenon and Streptomycin.—When a guinea pig has recovered from an infection with avirulent tubercle bacilli and become insensitive to tuberculin, reinoculation with a virulent strain produces an accelerated appearance of the tuberculin sensitivity. Streptomycin often produces extinction of tuberculin sensitivity in guinea pigs with experimental tuberculosis and an attempt was made to demonstrate this Willis phenomenon in such animals. Of 72 infected guinea pigs, 17 were left as controls, 55 were given streptomycin for 62 days starting three weeks after infection. At the onset of therapy all animals reacted to 10 mg. of tuberculin intradermally, 58 per cent had moderately or strongly positive reactions. One milligram of tuberculin produced reaction in 40 per cent of the animals. On the thirty-ninth day of treatment the tuberculin sensitivity had declined markedly; reactions to 10 mg. were much weaker and only 28 per cent reacted to 1.0 mg. On the sixtieth day no animal reacted to 1.0 mg.; 46 per cent showed very weakly positive reactions to 10 mg. Among these streptomycin-treated animals, 10 were chosen which did not react to 1.0 mg.; 6 of them gave no reaction to 10 mg. After reinfection with a virulent bovine strain these animals showed an accelerated reappearance of tuberculin sensitivity. The intensity of reaction was greater than that in 10 controls who were infected for the first time. In the streptomycin group, reactions were elicited on the seventh day after reinfection at a time when all 10 controls showed no reaction to 1.0 mg. and 6 did not respond to 10 mg. Two possible explanations are proposed for this observation: (*1*) in the cells of the desensitized animal there may be some sort of persistent latent sensitivity so that a very small additional dose of new antigen is necessary to build up a tuberculin

sensitivity which can be again objectively demonstrated; or (*2*) there may be a residual immunity in the desensitized animal with an increased ability of its phagocytes to destroy tubercle bacilli. The resultant rapid disintegration of bacilli at the site of superinfection might mobilize a massive dose of sensitizing antigen which would explain the rapidity of resensitization.—*Le phenomène de Willis après disparition de la sensibilité tuberculinique, A. Saenz & G. Canetti, Ann. Inst. Pasteur, July, 1949, 77: 89.*—(*V. Leites*).

Transmission of Streptomycin-resistant Tubercle Bacilli.—A 36-year-old Navy nurse had been assinged to a Streptomycin Study Unit since August, 1946. A routine chest roentgenogram in December, 1946 revealed no evidence of pulmonary disease other than a small calcified nodule. In February, 1947 the tuberculin reaction to purified protein derivative, first strength, was negative; the reaction to a half-strength solution of the second strength was questionable. In March, 1947 a chest roentgenogram showed a small, supraclavicular infiltration. During the following months the patient developed symptoms and the infiltration increased in size and excavated. Tubercle bacilli, cultured from the gastric content, grew readily in Dubos liquid medium containing as much as 1,000 γ of streptomycin per cc.—*Transmission of streptomycin-resistant tubercle bacilli in man, N. C. Furtos & E. A. Doane, J.A.M.A., August 20, 1949, 140: 1274.*—(*H. Abeles*)

Transmission of Streptomycin-resistant Tubercle Bacilli.—A hospital attendant, aged 32, developed a pleural effusion. Tubercle bacilli, isolated from the pleural fluid before the patient received any antibiotic treatment, were found to be resistant to 100 γ of streptomycin per cc. The probable source of infection was a patient with miliary tuberculosis admitted to the hospital where the attendant worked six months prior to his own illness. The tubercle bacilli cultured from the patient with miliary tuberculosis were sensitive to streptomycin prior to the initiation of treatment, but had become resistant to 500 γ of streptomycin after four months of treatment. This patient left the hospital two months before the onset of the attendant's symptoms.—*Streptomycin-resistant tubercle bacilli, isolation of resistant organisms from pleural fluid prior to institution of streptomycin therapy, A. J. Brennan & Ruth H. Wichelhausen, J.A.M.A., August 20, 1949, 140: 1275.*—(*H. Abeles*)

Streptomycin-dependent Tubercle Bacilli.—A simple method allowed the isolation of streptomycin-dependent tubercle bacilli from virulent cultures that had not previously been exposed to streptomycin. Tubercle bacilli of the H37Rv strain were grown in a flask of liquid sorbitan monooleate albumin medium until a turbid growth was obtained. The flask was shaken well and the number of viable cells was determined before enough streptomycin was added to the remaining undiluted liquid culture to give a final concentration of 100 γ per ml. of medium. Fifty plates containing 100 γ of streptomycin per ml. of solid oleic acid-albumin medium were each inoculated with approximately 280 million bacilli from the liquid culture. After 30 days' incubation, 62 colonies were found growing on the 50 plates; a total of 96 appeared during 70 days' incubation. There were 81 streptomycin-resistant colonies, 12 streptomycin-dependent colonies, and 3 colonies showing increased growth in the presence of streptomycin. The plates were incubated for longer than 70 days but no additional colonies appeared. A similar experiment was performed using a strain of *M. ranae* and, after 21 days' incubation of 50 plates, there were 40 colonies growing in the presence of 100 γ of streptomycin per ml. of medium. Of these, 27 were streptomycin-resistant and 13 streptomycin-dependent.—*Streptomycin-dependent tubercle bacilli: A simple method for isolation, D. Yegian, V. Budd, & R. J. Vanderlinde, J. Bact., August, 1949, 58: 257.*—(*F. G. Petrik*)

Streptomycin for Whooping Cough.—Streptomycin was administered to 129 children with whooping cough during a six-month period.

One hundred were less than one year of age. A series of 31 untreated controls was also observed. The drug was given by intramuscular injection, aerosol mist, nose drops, and by more than one route to various-sized groups; in 9 severely ill patients it was combined with hyperimmune serum. There was no toxicity from streptomycin and no evidence that the drug affected *H. pertussis*. It was believed that the intramuscular and aerosol usage had a favorable influence on the whooping cough but that no method was as effective as human hyperimmune serum.—*Streptomycin in treatment of whooping cough, L. W. Wannamaker, J. L. Kohn, & M. Weichsel, Am. J. Dis. Child., August, 1949, 78: 201.*—(*W. H. Oatway, Jr.*)

Streptomycin for Whooping Cough.—Earlier a favorable effect was reported when streptomycin was given by inhalation or intramuscular injection to infants and children with whooping cough. Another series has been studied in which more of the children were older. Children under three years of age were given the drug both by inhalation and intramuscular routes; children over three were given only the aerosol. Administration by both routes had no advantage over either method used alone. The effect on severely ill patients was variable. It was concluded that streptomycin has a favorable influence on the course of whooping cough. This is less marked in children over the age of one year.—*Further studies on the use of streptomycin in the treatment of whooping cough, K. S. Shepard, J. L. Kohn, S. R. Kaplan, & T. C. Allen, Am. J. Dis. Child., August, 1949, 78: 212.*—(*W. H. Oatway, Jr.*)

PAS in Experimental Tuberculosis.—Experimental tuberculosis was induced in guinea pigs with 0.001 mg. of a very virulent human strain. A number of animals received 0.03 to 0.1 Gm. of *p*-aminosalicylic acid (PAS) subcutaneously in a dilution of 1:5; another group was given the same doses in a dilution of 1:100. The animals treated with the concentrated solution showed no macroscopic visceral lesions on the eighteenth day. The spleen was small and smooth whereas untreated animals or those treated with the 1:100 solution showed definite tuberculous lesions of the spleen, which was hypertrophic. On the thirtieth day the untreated animals and those treated with the 1:100 PAS solution showed extensive macroscopic lesions in the spleen, liver, and lungs. In animals treated with the 1:5 solution the lesions in the spleen and the liver were much less pronounced and those in the lungs were almost absent after the same interval.—*Essai de traitement de la tuberculose expérimentale du cobaye par les formes hyperactives du PAS (para-amino-salicylate de sodium), J. Solomidès & E. Boulaud, Ann. Inst. Pasteur, September, 1949, 77: 310.*—(*V. Leites*)

Pulmonary Absorption.—The authors have undertaken a comprehensive study of the pharmacologic and mechanical aspects of direct medication of the human lung. This report deals with the pharmacodynamics of absorption and excretion of penicillin from the normal human lung; the results are compared with those of parenterally administered penicillin. Ten volunteers received 100,000 units of penicillin intramuscularly in 1.0 cc. of saline. The peak blood level occurred one-half hour after injection; the average level, at that time, was about one unit per cc. of serum. The level declined rapidly but significant levels were maintained for only three hours. Urinary excretion paralleled the blood levels. The total average urinary excretion was 47.24 per cent of the total injected. Nine subjects received 100,000 units of penicillin in 10 cc. of saline by the endotracheal route. After the cough reflex was suppressed by instillation of 2 per cent Pontocaine solution, the penicillin was administered through a tracheal catheter. The average blood level at one-half hour (0.14 unit per cc.) was one-eighth that obtained with the same dose administered intramuscularly. The levels continued to increase and reached their peak (0.17 unit per cc.) two hours after administration. At the end of three hours, the average level (0.11 unit per cc.) was almost

twice as high as the comparable intramuscular level (0.07 unit per cc.). Significant blood levels (0.04 unit per cc.) were maintained for twice as long as with intramuscular administration. Total urinary excretion was 15.9 per cent. Twelve subjects received 100,000 units of penicillin in 1.0 cc. of saline by aerosolization with the nebulizer-rebreathing bag apparatus. The average blood level at one-half hour was 0.12 unit per cc. At two hours, seven of the twelve serums showed significant levels. No significant levels were encountered after two hours. Total urinary excretion averaged 5.46 per cent. The results indicate that absorption from the alveoli is much slower than from muscle and that satisfactory blood levels can be achieved by the intratracheal route of administration which is not practical as a routine procedure. In chronic suppurative disease, parenterally administered penicillin does not reach the purulent sputum. High local concentrations are needed; for this purpose aerosolization by the nebulizer is a practical method which can be used at home. Following aerosolization 5.5 per cent of the penicillin is lost in the urine; 10.2 per cent is lost in the apparatus; 8 per cent is lost in the oropharynx; and 47.5 per cent is lost on expiration and other losses into the air. Thus one-third of the aerosolized penicillin actually reaches the lung. —*Pharmacodynamics of pulmonary absorption in man: I. Aerosol and intratracheal penicillin, E. A. Gaensler, J. F. Beakey, & M. S. Segal, Ann. Int. Med., October, 1949, 31: 582.—(H. R. Nayer)*

Putrid Empyema.—A 52-year-old man with putrid empyema and bronchopleural fistula was cured by intensive penicillin therapy without surgical drainage. Penicillin, 100,000 units in 50 cc. of normal saline, was instilled into the empyema cavity following aspiration of pus every 48 hours. Another 40,000 units were given intramuscularly every three hours and nebulized penicillin was inhaled for ten minutes each hour in concentration of 20,000 units per cc. Postural drainage was carried out several times daily. Culture of the pus revealed nonhemolytic *Streptococci* and *Aerobacter aerogenes*. The former was shown to be sensitive to 0.2 unit of penicillin per cc. After 4 penicillin instillations there was marked clinical improvement and no further fluid could be obtained on thoracentesis. Intramuscular and nebulized penicillin was continued for two weeks. The patient became asymptomatic and afebrile and roentgenograms revealed only thickened pleura. Fifteen weeks after discharge from the hospital, the patient was entirely well.—*A case of putrid empyema with a bronchopleural fistula successfully treated with penicillin, A. L. Forsgren, Ann. Int. Med., October, 1949, 31: 691.—(H. R. Nayer)*

Laboratory Studies

Growth of Tubercle Bacilli.—It was possible to view microscopically the growth changes in individual, virulent, human tubercle bacilli spread on the surface of a block of Sauton Tween agar medium in a specially prepared chamber. In general, observations were made daily for periods of six weeks. Nearly 100 per cent of tubercle bacilli added to such a system was observed to germinate. During the first 24 hours the cells increased in length and became curved. The curved cells then divided transversely and the two resulting cells gradually folded together until they lay side by side. Division occurred at a rapid rate beginning in the second 24-hour period and continuing for more than a week; by the third week growth had almost ceased. Growth in colonies, although less easily observed, appeared to follow a similar course of events. Branching forms rarely were observed. In other experiments streptomycin, penicillin, and sulfathiazole in various concentrations were incorporated into the agar medium of these chambers and observations were made after inoculation with tubercle bacilli. Studies with a wide range of concentrations of glycerin also were made. It was found that these agents were bactericidal in high concentrations and bacteriostatic when smaller amounts were present. With 2 units of streptomycin per ml. no growth occurred. Lysis of cells in this preparation was evident on the second day and was

complete by the seventh, with only fine granules remaining. With concentrations of 0.25 unit per ml. or less a bacteriostatic effect was observed; only a small percentage of the cells completed division although increase in length and curving of the cells was noted. Moreover, lysis of cells occurred during the succeeding days, the amount of destruction depending upon the concentration of streptomycin present in the medium. It was found that these effects also resulted after the addition of penicillin, sulfathiazole, or glycerin. It appeared that bacteriostasis and bacteriolysis followed the same pattern of occurrence, irrespective of which of these agents was present. An effect equivalent to 0.25 unit of streptomycin per ml. of medium was obtained with 80 units of penicillin per ml., 5 mg. of sulfathiazole per 100 cc., or a 10 per cent glycerin solution.—*Morphological studies of the normal growth of a human tubercle strain, and the effects of some antibacterial substances on same, E. Esperson, Acta path. et microbiol. Scandinav., 1949, 26: 178.—(V. Knight)*

Rate of Growth of Tubercle Bacilli.—The rate of growth of virulent tubercle bacilli can be estimated by a simple and relatively accurate method applicable to solid as well as liquid media. The practicability of the method was tested in the following manner: Suspensions of 14- to 21-day-old cultures of *M. tuberculosis*, H37Rv, were prepared and carefully diluted to obtain 8 suspensions containing 10^{-1} to 10^{-8} mg. of tubercle bacilli. Ten tubes, each containing 5.0 ml. of a modified Proskauer-Beck basal synthetic medium, were inoculated with each of the 8 quantities of bacilli making a total of 80 tubes in all. In addition, two modifications of the basal medium, one containing 0.2 per cent crystalline bovine albumin and the other 10.0 per cent sterile beef serum, were inoculated in the same manner. The time in days at which typical granular growth was first detected during incubation was plotted against the logarithm of the inoculum. The method is essentially an estimation of the rate of growth by a measurement of bacterial mass; the use of young, actively growing cultures as inocula minimizes the error due to a lag in multiplication on transference to a new medium. The method can be simplified by using only 3 sizes of inocula, for example, 10^{-3}, 10^{-4}, and 10^{-5} mg. of tubercle bacilli. The number of tubes inoculated with each quantity of tubercle also can be reduced to 5, but the tubes should be examined very carefully every day or at least every other day. *A method for the determination of the rate of growth of tubercle bacilli by the use of small inocula, G. P. Youmans & A. S. Youmans, J. Bact., August, 1949, 58: 247.—(F. G. Petrik)*

Growth Inhibition of Tubercle Bacilli.—The inhibition of growth of *M. tuberculosis*, H37Rv, by 5 analogues of phenylalanine and the effect of phenylalanine on this inhibition was investigated. The compounds studied were β-3-thienylalanine, β-2-furylalanine, α-aminophenylmethan sulfonic acid, and β-hydroxyphenylalanine. Proskauer-Beck synthetic medium was used for all of the compounds and additional tests were made with β-3-thienylalanine using as substrate Dubos sorbitan monooleate medium without albumin. The results show that 4 of the compounds inhibited the growth of the bacillus but phenylalanine overcame the inhibition with only 3 of them, β-3-thienylalanine, β-2-thienylalanine, and β-2-furylalanine. β-3-thienylalanine was by far the most effective of the analogues tested, 5 mg. per 100 cc. completely preventing surface growth in the Proskauer-Beck medium and 1 mg. per 100 cc. preventing growth in the sorbitan monooleate medium. With β-hydroxyphenylalanine at concentrations up to 100 mg. per 100 cc. no inhibitory action was observed. In addition to phenylalanine, the amino acids tyrosine, leucine, isoleucine, norleucine, and tryptophan counteracted the toxicity of β-3-thienylalanine although higher concentrations of these amino acids were required.—*Growth inhibition of tubercle bacilli by analogues of phenylalanine, H. Pope, J. Bact., August, 1949, 58: 223.—(F. G. Petrik)*

Air-borne Tuberculosis in the Rabbit.—Thirty-five rabbits of heterogenous origin were exposed to human-type tubercle bacilli in an improved Wells' apparatus. Twenty-nine animals received a primary air-borne infection, and 6 others were reinfected with the H37Rv strain. Three rabbits were killed early in the experiment; 25 of the remaining 26 animals developed a positive reaction to tuberculin, most of them within 17 to 36 days after exposure to infection. This reaction shortly diminished in intensity and only a few animals maintained a positive reaction until they were killed. Twelve animals killed within 84 days had small lesions which showed no predilection for any particular part of the lungs. Foci of necrosis were often present. Blood-stream dissemination was observed only once, to the spleen and kidney in a rabbit killed after 38 days. The tracheobronchial lymph nodes showed only microscopic lesions with minimal necrosis. Animals killed after 105 days had diseased areas which were more sharply circumscribed, caseated, and calcified; 6 had early local or bronchogenic dissemination; 5 had no spreading disease, and 5 others showed no gross or microscopic evidence of disease after 110 to 207 days. Only one of these 16 rabbits had detectable changes in the hilar nodes, but tubercle bacilli were cultured from them and from normal lungs. None of the 6 rabbits reinfected with 2,000 bacilli 73 to 87 days after the primary exposure showed lesions attributable to the re-exposure nor was the course of the disease induced by the primary infection modified. The tuberculin reaction sometimes returned or became more intense for a short time following reinfection.—*Quantitative air-borne tuberculosis in the rabbit, the course of human type infection, A. G. Hepplestion, J. Exper. Med., June, 1949, 89: 596.—(J. S. Woolley)*

Mice in Diagnosis of Tuberculosis.—This work was undertaken to evaluate the reliability of mouse inoculation tests with special emphasis upon their usefulness in the routine laboratory diagnosis of tuberculosis. The susceptibility of pigmented strains of mice (dba and C57) to tuberculosis induced by the intracerebral and intravenous inoculation of virulent human tubercle bacilli has been confirmed. In these studies, tubercle bacilli of the human, bovine, and avian types were of similar virulence for mice following inoculation by the intracerebral route. An acid-fast saprophyte failed to produce a progressive disease. In a comparative study involving a series of 25 strains of acid-fast bacilli there appeared to be a high degree of correlation between virulence for mice and virulence as measured by classical guinea pig tests. Preliminary studies indicated that a combination of rapid, diffuse growth in a liquid medium of the Dubos type plus subsequent mouse inoculation would reduce considerably the time required for the laboratory diagnosis of tuberculosis. Penicillin, added to a Tween albumin medium in a concentration of 2 units per ml. to suppress the growth of contaminants, proved to be toxic to the tubercle bacilli contained in experimental inocula consisting of digested and neutralized sputum specimens. Both treated (sodium hydroxide) and untreated routine clinical specimens were shown to be extremely toxic when inoculated intracerebrally directly into mice in an attempt to recover tubercle bacilli; therefore, the routine use of mice as a primary diagnostic procedure is not practical by the methods described. (Authors' summary.)—*The adaptability of mice to the laboratory diagnosis of tuberculosis, R. A. Patnode, M. M. Cummings, & G. A. Spendlove, J. Lab. & Clin. Med., August, 1949, 34: 1081.—(F. G. Petrik)*

Preservation of Gastric Specimens.—Some specimens of gastric juice have a bactericidal action on tubercle bacilli. This action is in direct proportion to the length of storage and can result in "false negative" culture reports, especially when specimens of gastric contents are sent through the mails. A study was undertaken to show the loss of positive results in stored specimens and to find a substance that would preserve tubercle bacilli in a viable state. Approximately 350 specimens of gastric contents were examined after storage, with or

without a preservative. The specimens were collected from patients with suspected early disease or with improvement following treatment; hence, the majority would be negative on culture. They represent the usual "gastrics" submitted, often by mail, for examination. One portion of each specimen was cultured within four hours of collection; the balance was stored for 24 to 48 hours under varying conditions. Both portions were treated as usual with sodium hydroxide and hydrochloric acid just before centrifugalization and inoculation onto 2 tubes each of Petragnani's and of Hohne's media. The number of positive cultures obtained was significantly reduced by storage for 24 hours, even at 4°C., when specimens were stored unaltered, after dilution with distilled or buffered water, or after neutralization with sodium bicarbonate. The addition of crystalline disodium phosphate before storage at room temperature increased slightly the number of positive cultures obtained after 24 hours and reduced insignificantly the number obtained after 48 hours.—*Culture of tubercle bacilli from specimens of gastric juice, P. Kabler & R. Lundholm, Am. J. Clin. Path., July, 1949, 19: 685.*—(*J. S. Woolley*)

Demonstration of Acid-fast Bacilli in Sputum.—A comparative study was made of various techniques for the microscopic detection of tubercle bacilli in 500 routine 24-hour specimens of sputum. About 10 ml. of distilled water was added to each specimen and very tenacious sputums were not included. After thorough mixing, 30 ml. from each specimen were mechanically shaken for fifteen minutes. Direct smears were made from all specimens before pipetting 5 ml. from each specimen into each of 5 large tubes. Each of the following concentration techniques was used on one tube in the series: (*1*) phenol-autoclave, (*2*) oxalic acid, (*3*) sodium hydroxide, (*4*) Clorox, and (*5*) trisodium phosphate. The sediment obtained was smeared on a slide after the addition of a drop of 1:4 dilution of serum to enhance fixation. After staining with the Ziehl-Neelsen technique, 100 oil-immersion fields were examined on each slide. Of the 500 specimens examined, 374 (75 per cent) were found positive for tubercle bacilli. With the trisodium phosphate technique, 374 specimens gave positive results; with the Clorox technique, 371; with the direct smear technique, there were 339 positive specimens. Although the number of positive smears with the most successful technique was only 7 per cent greater than that with the direct smear method, the number of detectable tubercle bacilli on each slide was increased by the concentration procedures. The trisodium phosphate technique has the advantages that the material preserves viable tubercle bacilli for as long as one week at 37°C. and does not have to be neutralized. —*Use of Clorox and trisodium phosphate in demonstration of acid-fast bacilli in sputum, M. S. Tarshis & W. G. Lewis, Am. J. Clin. Path., July, 1949, 49: 688.*—(*J. S. Woolley*)

Mycobacterium paratuberculosis.—Two groups of sheep were injected with various quantities of dead *M. paratuberculosis* suspended in mineral oil. Their serological response was checked by testing their sera for complement-fixing antibodies using antigens from infected intestinal tissue. The development of allergy as manifested by cutaneous reaction to avian tuberculin was also noted. One injection of 0.1 ml. of commercial avian tuberculin was used and the reaction was read 48 hours after the injection. The results indicated that all the different doses elicited a maximal serological and allergic response since the antibody titers and allergy produced by 5 mg. of bacilli were just as great as those produced by larger doses. The difference in the temperatures at which the bacteria were killed was not seen to influence the experimental results. A second injection was given to one-half of the sheep employed in the first experiment fifteen months after the first injection, and one-half of the sheep in the second experiment twelve months after the first injection. The second injection did not noticeably influence the level of complement-fixing antibodies or the allergic state in these experimental sheep. The possibility that injections of this

"vaccine" will increase the resistance to natural injections is now being investigated.—*Immunization with heat-killed Mycobacterium paratuberculosis in mineral oil, B. Sigurdsson & A. G. Tryggvadottir, J. Bact., September, 1949, 58: 271.*—*(F. G. Petrik)*

Bactericidal Action of Triethylene Glycol.—The bactericidal effect of triethylene glycol on Streptococci, Pneumococci, and Staphylococci was studied under varying conditions of atmospheric humidity and concentrations of glycol vapor using specially constructed experimental rooms with controlled relative humidity, vapor concentration, and temperature. The bacterial content of the air was estimated by bubbler samplers and sedimentation plates, the former suitable for fine particles suspended in the air, the latter for larger droplets. It was found that, when the relative humidity was between 15 and 40 per cent, a 50 to 100 per cent saturation of the air by glycol vapor killed 30 to 90 per cent of the bacteria suspended in the air in the first two minutes; in the next two minutes, the air was essentially sterilized. As the relative humidity rose above 50 per cent, the bactericidal effect of the vapor diminished markedly. The air-sampling by sedimentation plates revealed that the larger particles are even less susceptible to glycol vapor at relatively high humidity than the smaller particles.—*The rate of bactericidal action of triethylene glycol vapor on microorganisms dispersed into the air in small droplets, W. Lester, Jr., O. H. Robertson, T. T. Puck, & H. Wise, Am. J. Hyg., 1949, 50: 174.*—*(Max B. Lurie)*

Pulmonary Function.—The accurate evaluation of partial disability due to silicosis is a difficult problem. Dyspnea which is commonly employed as an index of disability may be produced by a combination of pulmonary and circulatory factors. Disability tests which are based entirely on the ventilatory component of respiration are not satisfactory; accurate results require measurement of both the ventilatory and respiratory components of breathing. The ventilation equivalent is a figure stating the number of liters of air breathed through the lungs from which 100 cc. of oxygen is absorbed or in which 100 cc. of carbon dioxide is exhaled to each 100 cc. of air breathed; it measures both components. The ventilation equivalent for oxygen, used alone, decreases greatly during intentional hyperventilation and may therefore be unreliable. The equivalent for carbon dioxide changes much less during intentional hyperventilation. The author devised a technique which determines both equivalents simultaneously while the subject is at rest, exercising, and recovering from exercise. The results are charted on a graph where the oxygen equivalent is plotted against the simultaneous carbon dioxide equivalent. Any point on this graph also determines the respiratory quotient. The normal values for oxygen equivalents are above 3.4 and for carbon dioxide above 2.9. This technique was employed on 20 normal subjects, 56 patients with pathologic conditions of the chest and circulation other than silicosis, and 30 patients with pneumoconiosis. By using the author's graph, it is possible to exclude all errors due to intentional hyperventilation since the plotted points fall uniformly below the line where R.Q. equals 1. The continuous recording permits the observer to follow in detail the behavior of the equivalents during exercise and recovery. Characteristic curves are obtained in normals and in varying degrees of pathologic conditions of the lungs and circulation. Measurements taken at rest alone are not as reliable as those taken at rest, during exercise and recovery. The results obtained by this method do not correlate well with roentgenologic findings but do correlate well with the degree of dyspnea of the patient and with the impairment of efficiency manifested during the patient's usual activities.—*A new method of evaluating disability in silicosis and in other conditions of the lung and circulation, P. Pelnáru, J. Indust. Hyg. & Toxicol., September, 1949, 31: 264.*—*(H. R. Nayer)*

Public Health and Epidemiology

BCG Vaccination.—The original strain of BCG was received in China from Paris in 1936 and a special department was created to

culture it. This work has been kept completely independent of other departments and laboratories to avoid contamination. Persons working in the BCG laboratories are free from tuberculosis and precautions are taken to avoid sources of contact. Before use the stock culture is tested on laboratory animals for virulence. Vietsin (sodium glutamate), a condiment in Chinese cooking, was employed from 1942 to 1945 instead of asparagin as an essential ingredient of Sauton's medium. It satisfactorily maintained the stability of the BCG culture. Since 1937, BCG vaccine has been prepared once weekly. With this material 7,511 children were vaccinated by the oral route, but tuberculin tests were not done. No harmful effects have been noted among those newborn babies vaccinated. An additional 2,140 children were vaccinated by parenteral routes. Of those receiving vaccine intracutaneously, 90 per cent were converted from tuberculin-negative to positive. An abscess developed at the site of vaccination in 8 per cent. Of those children vaccinated by the scarification method, using a concentration of 75 mg. of BCG per cc., 97 per cent of the negative tuberculin reactors became positive. There were no ill effects with this method. No tuberculous morbidity or mortality has been reported among those vaccinated with BCG manufactured by the Shanghai Pasteur Institute.—*BCG vaccination—eleven years of experience, Y. C. Licou & C. C. Kouo, Chinese M. J., May, 1949, 67: 275.—(B. Hyde)*

Tuberculin Patch Tests.—Studies have been made to identify any conditions which may modify the efficiency of patch tests. It was found that the patch became less efficient with age, with a decrease in the "patch sensitivity quotient" from 0.92 after one and one-half years to 0.74 at six years. Removal of the patch at 24 hours reduced the efficiency; reapplication of the patch or prolonged contact accentuated it. Streptomycin applied to the patch had no effect on the reaction, nor did the presence of a fever. Repeated patch tests on nontuberculous infants did not stimulate sensitivity, and multiple tests caused a constitutional reaction only once.—*Tuberculin patch test, J. Schwartzman & M. Cerone, J. Pediat., August, 1949, 35: 185.—(W. H. Oatway, Jr.)*

Pseudoreactions to the Patch Test.—Tuberculin patch tests have been reported to produce pseudoreactions but they are extremely rare. The author has seen but 11 instances during a period of ten years. The pseudoreactions must be distinguished from several cutaneous changes due to application of the test including discoloration by tuberculin, hypersensitivity to adhesive in areas contiguous to the patches, miliaria from perspiration, and a very rare sensitivity to the media. Actual pseudoreactions have the same distribution as a positive patch test. They differ from true reactions in that they usually occur in persons with a personal or family history of allergy; they appear and fade more rapidly; and they appear to be an irritated, erythematous, nonindurated dermatitis. Late readings, four to seven days after removal of the patch, show pseudoreactions to have faded while true reactions are still visible. The major portion of known pseudoreactions occurred during the war when a lower temperature than usual was used for concentration of the tuberculin. Apparently an offending substance is eliminated by the higher temperatures.—*Pseudoreactions to the tuberculin patch test, H. Vollmer, Am. J. Dis. Child., September, 1949, 78: 302.—(W. H. Oatway, Jr.)*

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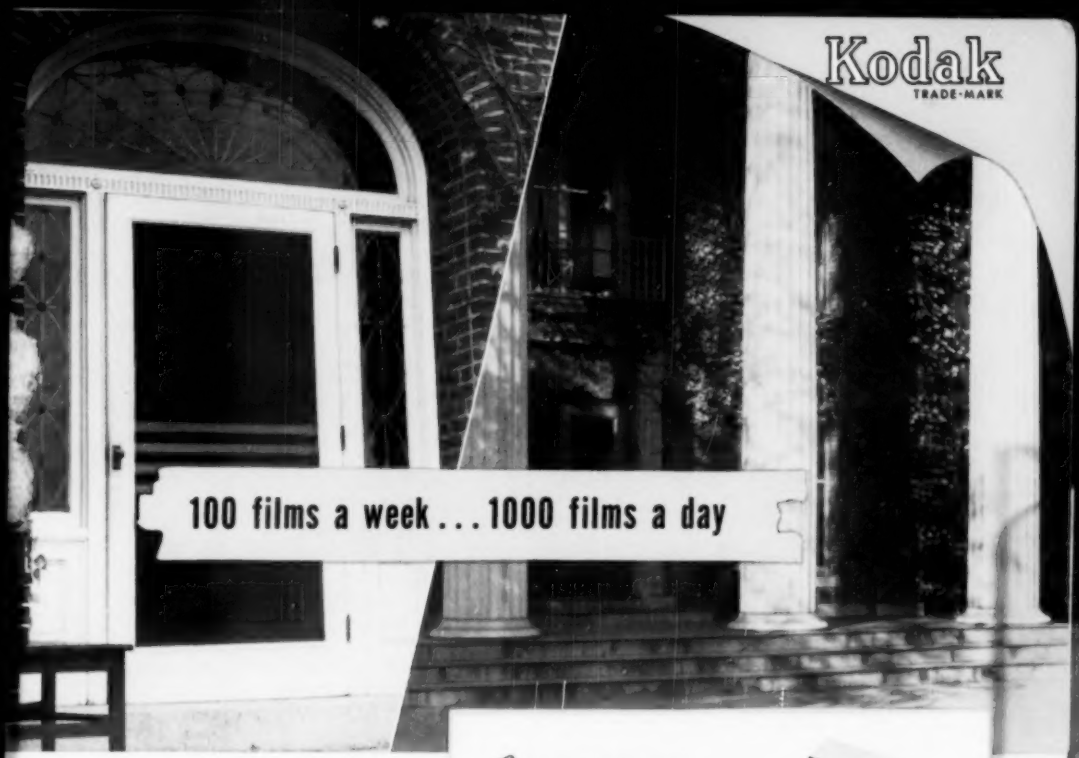

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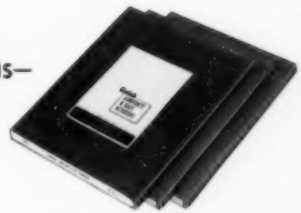

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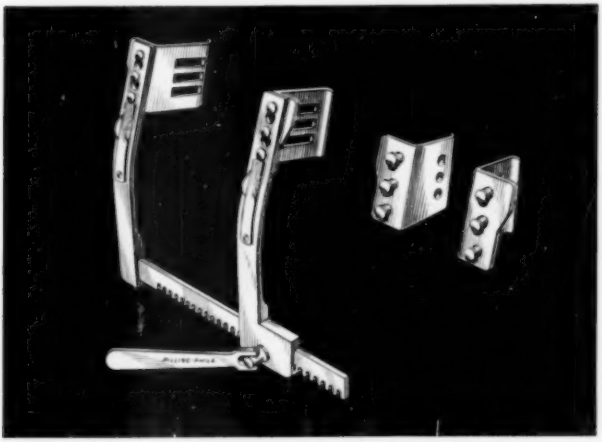

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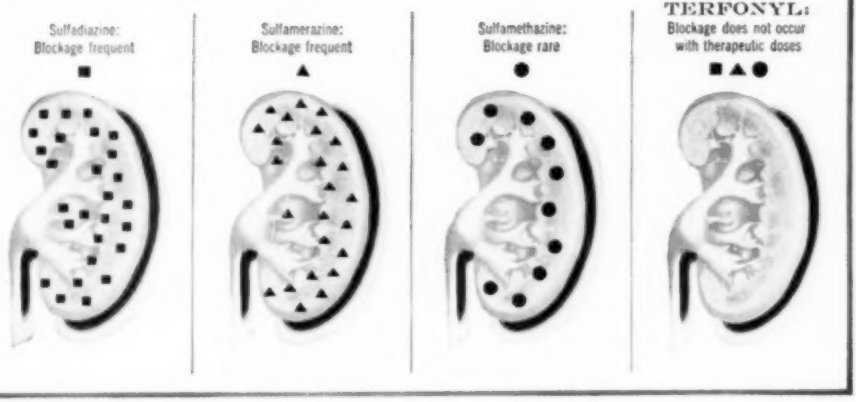

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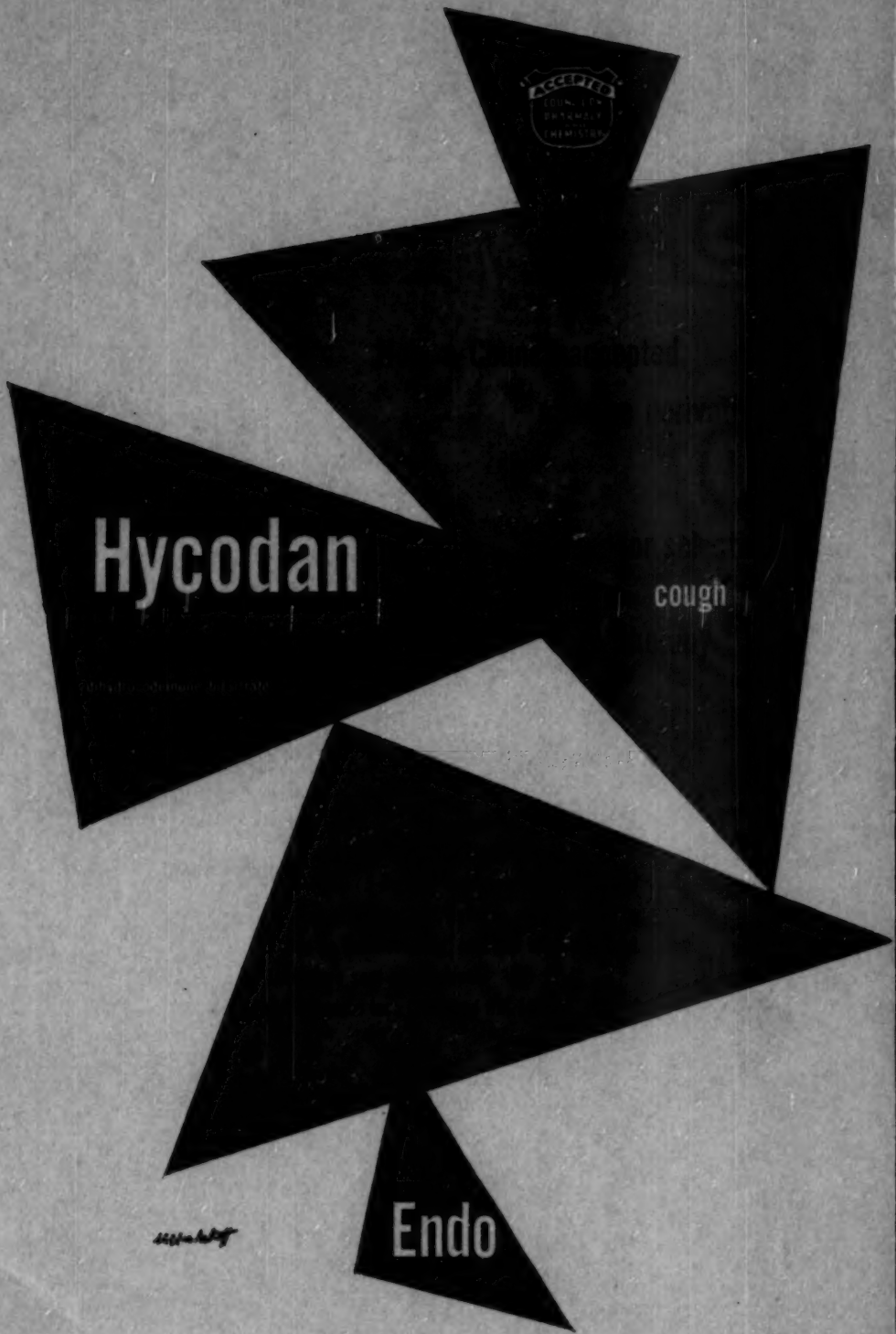
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